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A CLINICAL AND PATHOLOGICAL STUDY OF SUBACUTE AND CHRONIC GLOMERULONEPHRITIS, INCLUDING LIPOID NEPHROSIS *

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In a previous report [1] the various types of acute nephritis were described. This publication is based on a study of 181 cases which have been classified in accordance with certain clinical and pathological features as follows:

Group I. Subacute glomerulonephritis, 16 cases.

Group II. Chronic glomerulonephritis in which death was due to an intercurrent disease, 8 cases.

Group III. Advanced chronic glomerulonephritis of azotemic type, 117 cases.

A. With a history of acute glomerulonephritis, 30 cases.

B. No history of acute nephritis; kidneys weighing together 250 gm. or more, 33 cases.

C. No history of acute nephritis; kidneys weighing together less than 250 gm., 54 cases.

Group IV. Chronic glomerulonephritis of the hydropic type, 40 cases.

A. With the glomerular structure of chronic proliferative glomerulonephritis, 6 cases.

B. With a glomerular structure largely of membranous but partly of proliferative type, 9 cases.

C. With a normal glomerular structure or a membranous type of glomerulitis, 25 cases.

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The distribution of the cases by groups and by decades is shown in Table I. It is to be noted that this is the age at death and not the time of onset of the disease. When a complete history is available it is usually found that the disease has been present a number of years. In the 30 cases of the chronic azotemic type in which the complete course of the disease is known (Table IV) the average age of onset is 20 years and the average age at death 30 years. About two-thirds of the patients die between the ages of 20 and 50 years, and since most of them are under treatment only during the advanced stages, the grouping shown in Table I cor-

TABLE I

Frequency and Age Distribution of Nephritis

Age	Total number of autopsies	Groups				Total
		I	II	III	IV	
yrs.						
0–10	4,710	1	0	1	9	11
10–20	1,103	3	0	10	3	16
20–30	2,186	3	2	30	6	41
30–40	2,032	2	1	33	10	46
40–50	4,000	2	1	23	6	32
50–60	4,151	3	2	10	3	18
60–70	4,076	1	0	8	2	11
70–80	2,590	1	1	2	1	5
80–90	700	0	1	0	0	1
90–100	50	0	0	0	0	0
Total	25,598	16	8	117	40	181

responds fairly well with patients under observation. The disease is by no means limited to children and young adults, although it is probable that a majority of the cases have their onset during these periods. There are, however, instances in which the disease begins in middle life or later. In our experience about one-half of the cases of fatal nephritis in children under 10 years of age are the hydropic type (lipoid nephrosis).

Frequency: It appears in Table I that the forms of nephritis under discussion are relatively rare and comprise only about 0.7 per cent of the total mortality. Chronic Bright's disease, which includes hypertensive renal insufficiency as well as all forms of chronic glomerulonephritis, causes only a little over 1 per cent of all deaths. The high incidence of nephritis in vital statistics is

due to the inclusion of a large number of cases of primary hypertension with albuminuria and edema resulting from myocardial failure.

Sex: In the entire group studied there were 105 males and 76 females, but in the postmortem series there are approximately twice as many males as females over 30 years of age. When a correction is made for this factor there seems to be no predominance of either sex.

Group I. Subacute Glomerulonephritis (Table II).

This group blends on the one side with the acute and on the other with the chronic type, and the limitations are somewhat arbitrary. Clinically cases that terminate in uremia after a course of a few months duration are usually called subacute. Pathologically fairly definite diagnostic criteria have been established. The kidneys are not contracted; they are either of normal size or enlarged. Microscopically one finds a severe and uniform obstruction of all the glomeruli, but there are no hyaline glomeruli (Fig. 1). There is a moderate uniform atrophy of all the tubules. Subacute nephritis is distinguished from the acute form by the presence of moderate tubular atrophy; there is very little atrophy in the acute type. It is distinguished from chronic nephritis by the moderate uniform tubular atrophy and the absence of hyaline glomeruli; in the chronic form there are patches of extremely atrophic tubules associated with hyaline glomeruli (Fig. 5).

The 16 cases listed in Table II were identified by their pathological features but the clinical duration was known accurately in nearly all of them.

Example of Subacute Glomerulonephritis (Case 2, Table II)

Clinical History: A boy, 16 years of age, was admitted to the hospital Sept. 16, 1937. There was no history of scarlet fever. He had had occasional attacks of sore throat, but there had been no infection of any kind during the year preceding his present illness. In the latter part of June, 1937, he first noticed a slight swelling of the face and ankles, otherwise he was well at this time. About July 9th, he began to feel drowsy and weak; the swelling of his face and ankles had not increased. He consulted a physician who diagnosed nephritis. In August he spent 2 weeks in a hospital under the diagnosis of acute nephritis. About September 5th a generalized anasarca developed, with weakness, headache, vomiting and drowsiness. After September 11th he noted a disturbance of vision and oliguria.

TABLE II

Group I. Subacute Glomerulonephritis

Case No.	Autopsy No.	Age	Sex	Duration	Blood pressure	Albuminuria	Edema	Urea nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Epithelial crescents	Comment
		yrs.		*mos.*	*mm. Hg.*			*mg./100 cc.*	%	*gm.*	*gm.*		%		
1	25–798	8	F	2	—	—	2	—	—	149	224	0	—	4	
2	37–1830	16	M	3	192/112	4	3	77.8 (1 day)	—	360	710	0	50	2	Casts. Plasma proteins 4.2 gm. %
3	30–1567	16	M	7	180/114	4	3	116 (1 wk.)	0 (1 wk.)	320	285	0	45	1	Retinitis
4	31–1508	17	F	6	200/112	—	3	56.4 (1 mo.)	—	390	225	2	—	1	Retinal detachment
5	18–118	21	M	7	140/80	+	2	14 (6 mos.)	15 (6 mos.)	375	425	1—	—	3	
6	18–237	22	F	4	220/120 (1 wk.)	3	3	33 (12 days)	—	300	260	2	—	3	
7	13–8	26	F	3	—	+	1	—	—	Normal	Normal	0	—	4	Marked hematuria
8	12–131	33	M	3+	—	+	1	—	—	460	415	2	—	1	
9	16–368	39	M	5	—	3	3	104 (1 day)	0 (1 day)	375	280	0	35	2	
10	25–945	41	M	2	248/102	1	2	80 (7 wks.)	10 (7 wks.)	—	335	0	—	0	Embolic type
11	22–554	43	M	6	140/60 (1 day)	3	1	119 (1 day)	—	610	270	3	—	0	Embolic type, aortic endocarditis
12	15–253	51	M	4	172/100	2	3	—	—	375	500	—	—	0	
13	19–5	55	M	12	200/120	+	1	—	0 (1 day)	420	520	0	—	1	Retinitis
14	30–415	57	M	3	150/95 180/100	4	3 2 0	140 (6 wks.)	2 (10 wks.)	430	360	1	50	1	Retinitis
15	29–1799	62	M	1	190/110	4	1	190 (2 wks.)	—	—	550	0	48	1	Edema of retina
16	11–77	70	M	—	—	+	3	—	—	475	335	0	—	3	

The percentage of phenolsulphonephthalein excreted in 2 hours is shown. Numerals are used to indicate the intensity of albuminuria, edema, passive congestion of the liver and the extent of formation of epithelial crescents. The time before death is indicated in some of the observations. The — sign means no observation.

On admission, Sept. 16, 1937, a severe generalized anasarca was noted. There was dyspnea, with evidence of edema of the lungs and ascites. The temperature was subnormal and the heart rate was rapid and regular. The eyegrounds showed a grayish exudate but the retinal arteries appeared normal. The blood pressure was 192/112 mm. Hg. The total diuresis for 24 hours was only 45 cc. Death occurred on Sept. 18, 1937.

Laboratory Examinations: Hemoglobin 50 per cent; red cell count 2,700,000; leukocytes 12,900 — 84 per cent neutrophils; blood urea nitrogen, 77.8 mg. per cent; carbon dioxide combining power of the blood, 16 per cent. Plasma proteins: albumin 2.2, globulin 2 — total protein 4.2 gm. per cent.

In subacute glomerulonephritis the blood pressure usually rises steadily and is commonly very high in the advanced stages. Disturbances of vision from retinal edema or hemorrhages are frequent.

The urine contains abundant albumin and casts. The specific gravity often decreases, and oliguria is frequently a prominent feature. Hematuria is infrequent.

Edema is usually rather well marked and was not absent in any of our cases. The plasma proteins were determined in only 1 case (Case 2), and their low level is an ample explanation of the edema in this instance. Cardiac failure may have been a contributory cause of edema in Cases 4, 6, 8 and 11, since there was a definite chronic passive congestion of the liver in each of these. In Case 11 the associated heart disease was presumably the cause of the severe passive congestion of the liver. Probably the low level of the plasma proteins is the chief cause of edema, since edema was present in 9 cases in which there was no passive congestion of the liver. A high venous pressure is a more delicate indication of cardiac failure than passive congestion of the liver, but this observation was not available.

Renal insufficiency may always be demonstrated if tests are made in advanced stages of the disease. Death was apparently due to uremia in all of our cases. As in other forms of uremia, the hemoglobin decreases as renal insufficiency develops.

The heart is usually only moderately enlarged. Omitting the 8 year old child (Case 1) and the case of endocarditis (Case 11) the average weight of the heart was 389 gm. Apparently hypertension must be maintained at a high level for a long time before marked cardiac hypertrophy develops.

The kidneys are of normal size or moderately enlarged, but

occasionally they are very large (Case 2). The average combined weight of the kidneys in 15 cases is 380 gm., but if Case 2 be omitted the average weight of the remaining 14 cases is only 356 gm. The external surfaces are smooth and on section the cortices are of normal or increased width. Microscopically, as noted above, there is found a uniform diffuse tubular atrophy (Fig. 1). There are no islands of normal tubules, as in chronic nephritis, and the tubular atrophy is not extreme. Since all the tubules are involved it is obvious that the patient cannot survive to the point of extreme tubular atrophy such as one finds in parts of the cortex in chronic nephritis. The glomeruli are uniformly involved and severely obstructed. There are no solid hyaline glomeruli, since the process is too recent, but there may be small hyaline areas in the centers of some of the glomerular lobules. Epithelial crescents may play a rôle by compressing the glomeruli, but the most important cause of glomerular obstruction is endothelial proliferation.

There are different histological types. In the usual proliferative form the centers of the glomerular lobules consist of a dense mass formed by splitting and fusion of the central capillary basement membranes. This central mass may show beginning hyaline degeneration. The peripheral zones of the glomerular lobules contain narrow capillaries which are, however, insufficient in number and caliber to afford adequate filtration. Decreased glomerular filtration results in partial disuse atrophy of the tubules.

In Cases 1 and 7 the glomerular obstruction was due largely to epithelial crescents. In Cases 10 and 11 the lesions were all of embolic type, and in 1 of these, Case 10, no endocarditis was present. These 2 cases might also be classified as embolic glomerulonephritis, but lesions of embolic type frequently occur independently of endocarditis. Occasionally uremia is due in part to extensive tubular obstruction by casts as in Case 2.

Group II. Chronic Glomerulonephritis in which Death was due to an Intercurrent Disease (Table III)

The 8 cases listed in Table III are examples of chronic glomerulonephritis in which death was caused by another disease before marked renal insufficiency had developed. These cases are of particular interest since little is known of the structural changes

TABLE III

Group II. Chronic Glomerulonephritis in which Death was due to an Intercurrent Disease

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Albuminuria	Edema	Urea nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Hyaline glomeruli	Tubular atrophy	Cause of death
		yrs.			*mm. Hg.*			*mg./100 cc.*	%	*gm.*	*gm.*		%	%		
17	24–807	20	F	7 mos.	138/86 158/98	2	1	49.4 (6 mos.) 15.5 (8 days)	47 (5 days)	400	465	—	40	0	0	Streptococcic bacteriemia
18	31–794	22	F	3 yrs.	140/90 (3 yrs.) 150/90 (5 days)	4	0	—	61 (3 yrs.)	—	Large	1—	—	10	1—	Tetanus following induced abortion
19	33–292	34	F	2 mos.+	170/90	4	1	28 (2 days)	—	420	462	3	70	10	1_d	Ulcerative colitis, encephalomalacia
20	27–511	43	F	1 yr.	110/70	1—	1	—	—	538	304 (one)	1	—	0	0	Cardiac failure
21	25–146	51	F	4 yrs.	—	1	0 3	29.5 (2 wks.)	—	240	190	—	90	0	0	Bronchopneumonia
22	28–1110	58	F	4 yrs. (?)	—	1—	0 2	—	—	215	195	1—	40	0	0	Marked emaciation, ischiorectal abscess
23	31–748	70	F	4 mos.+	170/100	2	3	Normal (1 wk.)	—	606	438	2	34	20	1	Cardiac failure
24	34–1408	80	F	? yr.	138/60	1	1	15.6 (1 day)	—	450	250	0	58	5	1	Purulent bronchitis, pericarditis

Explanations as in Table II. 1_d = diffuse tubular atrophy of mild degree.

in the kidneys during the long interval between the primary acute attack and the terminal chronic stage.

The diagnosis of glomerulonephritis in this group is based entirely on the microscopic structure of the kidneys except in Cases 17 and 18 in which it was also established clinically. In the other 6 cases the renal symptoms were overshadowed by those of the major illness. In Case 19 the clinical picture was that of ulcerative colitis with severe albuminuria and mild edema. In Case 20 the clinical impression was cardiac failure. In Case 21 there was a history of dyspnea and palpitation for 4 years, and a general anasarca developed during the last month of life. In Case 22 there was an ischiorectal abscess of 4 years duration, as well as severe emaciation. There was only a trace of albumin in the urine and the edema developed terminally. Case 23 was a typical example of hypertension with cardiac failure.

There was a very slight elevation of the blood urea nitrogen in Cases 19 and 21, but there was no clinical or anatomical evidence of serious impairment of renal function in any instance.

The clinical history in Case 18 will be given in detail since this case is a good illustration of the group under discussion. I am indebted to Dr. George Fahr for the excellent clinical record which follows.

The patient, an unmarried woman, 19 years of age, was admitted to the hospital Feb. 15, 1928, complaining of a cold, sore throat, headache and swollen cervical lymph nodes. The diagnosis was acute tonsillitis. On February 27th the urine contained albumin ++++, the leukocyte count was 13,300, and the blood pressure was 140/90 mm. Hg. The 2 hour excretion of phenolsulphonephthalein was 61 per cent. There was no edema. The diagnosis was acute glomerulonephritis. The patient gradually improved. On March 1st, the leukocyte count was 8700 and the blood pressure on March 7 was 126/84 mm. Hg. Tonsillectomy was performed on March 13, 1928, and the patient was discharged on April 19, 1928.

She was readmitted on Oct. 8, 1928, with symptoms of sinusitis. The urine showed albumin ++; the leukocyte count was 9050; and a concentration-dilution test gave a range of specific gravity from 1005 to 1023. The clinical diagnosis was now chronic glomerulonephritis, which was regarded as the outcome of the attack of acute glomerulonephritis in the preceding February. The patient was discharged after a few days and continued her work as a nurse in apparently good health until the onset of her final illness on May 1, 1931.

She was readmitted to the hospital May 1, 1931, suffering from acute endometritis following an induced abortion. Tetanus developed and death occurred on May 6, 1931. There was albuminuria but no edema. The blood pressure was 150/90 mm. Hg. No functional studies were made at this time.

At postmortem the kidneys were found to be enlarged with smooth external surfaces. Microscopically about 10 per cent of the glomeruli are hyaline, and there is atrophy of their associated tubules. Practically all of the other glomeruli present a similar appearance. They are slightly enlarged and their lobulations are distinct (Fig. 2). Under higher magnification the lobules show solid central portions with small peripherally situated capillaries (Fig. 3). There is some increase of endothelial cells but the capillaries are not markedly constricted. The peripheral capillary basement membranes are not thickened. Glomerular filtration is evidently fairly good since there is no atrophy of the tubules associated with these glomeruli.

The structural changes in the kidneys of the other 7 cases in Group II correspond to the above description aside from minor variations. The kidneys are not contracted but are usually somewhat enlarged. In Case 19 there were some epithelial crescents, the capillary obstruction was more pronounced than is shown in Figures 2 and 3 and had resulted in a slight tubular atrophy. In Case 21 the glomerular lesions were less intense than in Case 18. In Case 23 an arteriolosclerosis was present which was responsible for most of the hyaline glomeruli.

We may now trace the pathogenesis of the glomerular lesion in chronic glomerulonephritis. The normal glomerular lobule is composed of capillaries with a distinct basement membrane in both inner and outer walls (compare Figs. 3 and 4, Plate 130, *Am. J. Path.*, 1936, **12**, 801–824). In acute glomerulitis there is an increase of endothelial cells and the central basement membranes of the capillaries are split into numerous irregular fragments which have been called intracapillary fibers. In severe glomerulitis the capillaries are completely obstructed, but in the less severe lesions (Fig. 4), from which the chronic forms probably develop, the capillaries are not closed completely. As the inflammation subsides the blood forces the intracapillary fibers to the center of the lobule where they become fused to form a central hyaline mass and the lobule then has the appearance shown in Figures 3 and 7. If the capillaries are completely closed during the acute attack the glomerulus becomes hyaline. The functioning glomeruli in chronic azotemic glomerulonephritis usually resemble those shown in Figures 2 and 3. The most important difference between the

early or mild lesions of Group II and those of advanced azotemic glomerulonephritis is that in the latter group nearly all the glomeruli have become hyaline; the persistent functioning glomeruli in the advanced stage are not notably different in structure from those of the early stage. One may well believe that the progress from the early to the advanced stage of chronic glomerulonephritis is due to repeated acute attacks which obstruct more and more of the glomerular circulation.

The only publication known to me which deals with the structure of chronic glomerulonephritis in the pre-uremic or latent chronic stage is one by Dorothy Russell [2] in 1934. She described a kidney removed under an erroneous diagnosis 16 years before death. The remaining kidney at autopsy showed a typical advanced chronic glomerulonephritis. The illustration of the kidney removed 16 years before death is shown only under low magnification but resembles those of Group II.

Group III. Advanced Chronic Glomerulonephritis of the Azotemic Type (Tables IV, V and VI)

This group, which comprises 117 cases, has been divided into 3 subgroups in accordance with certain clinical and pathological features. Subgroup A (Table IV) includes 30 cases in which there was a definite history of acute glomerulonephritis. Subgroups B and C (Tables V and VI) include 87 cases in which no history of an acute attack was obtained; in the former the kidneys weighed together 250 gm. or more, in the latter they weighed less than 250 gm. and showed varying degrees of contraction. It will appear that the separation of subgroups B and C has little clinical significance but it will serve to emphasize certain structural differences between large and small kidneys.

Considering Group III as a whole we may call attention to certain features.

Duration: The total course of the disease is known only in the 30 cases listed in Table IV. In this group the duration ranges from 18 months to 26 years. The average time between the acute attack and death is 10 years. The duration is as follows: under 5 years, 8 cases; 5 to 10 years, 9; 10 to 15 years, 5; 15 to 20 years, 5; 20 to 26 years, 3.

The acute attack is often followed by a latent period during

which the patient considers himself well, although it is probable that symptoms and signs of the disease could be detected by careful examination. As shown in the table, the latent period may last many years (Case 54, 24.5 years; Case 46, 23.5 years; Case 39, 14 years). However, the active chronic stage may begin immediately after the acute stage, *e.g.* Cases 29, 32 and 35.

The duration shown in Tables V and VI is merely the length of the active chronic stage in most of the cases. It is measured from the date of onset of symptoms as given by the patient except in a few cases in which it is dated from the finding of albuminuria in the course of an examination for life insurance. It is remarkable that 16 patients worked at their usual occupations and considered themselves in good health up to a period from 1 month to 3 months before death, although the kidneys at postmortem often showed a high degree of contraction indicating a duration of many years. It is clear that the duration of symptoms is far less than the total course of the disease. The average duration in the group in which the complete history is known (Table IV) is 10 years, while in those with no history of acute onset (Tables V and VI) it is only 3 years.

Frehse,[3] in a study of 248 cases of nephritis, found that 68 lasted over 5 years, 23 over 10 years, 19 over 15 years, 6 over 20 years, and 3 over 40 years.

The Acute Attack: In most instances the acute attack was typical and fairly severe, confining the patient to bed for a number of weeks, but in some cases it was mild and characterized only by headache with albuminuria or edema. It is easily possible that in the cases with no history of acute glomerulonephritis there was a mild attack that was not recognized as nephritis. For example, in Case 18 the condition following the attack of acute tonsillitis would not have been recognized as acute glomerulonephritis if a careful study had not been made. It is the usual experience that in a majority of the cases first seen in the active chronic stage careful inquiry does not reveal an illness which can be interpreted as acute glomerulonephritis. On the other hand, patients first seen in the acute stage and subsequently followed for a number of years show all the variations in the clinical course that appear in Table IV. Some of them pass directly into the active chronic stage and others remain in fairly good health for a number of years.

TABLE IV

Group III. Subgroup A. Chronic Azotemic Glomerulonephritis with a History of Acute Glomerulonephritis

Case No.	Autopsy No.	Age	Sex	Total duration	Duration of active chronic	Initial infection	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.		*yrs.*			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%					
25	35–2064	15	M	4	4 yrs.	—	220/110	—	285 (1 day)	—	380	460	o	59	2 o	—	o	b_1	
26	36–2149	15	F	1.5	18 mos.	Tonsillitis	148/100 (18 mos.) 170/130	34 (18 mos.) 118 (1 day)	—	49 (18 mos.) o (1 day)	450	160	2	54 (18 mos.)	1 4	—	o	a	Plasma proteins 5.5 gm. %
27	25–246	16	F	4	16 mos.	Sore throat	180/130	70 (1 mo.)	—	o (1 mo.)	400	163	1—	38	2 1	+	2	a	
28	23–846	18	M	2	1 mo.	—	200/134	181 (2 days)	—	—	475	245	1—	50	1	+	3	a_2	
29	31–1974	19	M	9	9 yrs.	Scarlet fever	180/110	110 (1 mo.) 238 (1 day)	—	—	550	200	o	28	1 o	—	1	a	
30	34–763	19	F	4	4 yrs.	Common cold	180/148 (5 mos.)	—	102 (1 wk.) 218 (1 day)	20 (5 mos.)	350	150	2	46	2 o	+	2	a	Exacerbations
31	36–1587	20	M	10	2 yrs.	Common cold	190/125 (1 mo.)	—	171 (1 mo.)	—	585	180	o	35	1 3	+	o	a	
32	33–1180	21	F	14	14 yrs.	Scarlet fever	160/100 (4 mos.)	—	327 (2 wks.)	2 (4 mos.)	325	100	1	35	2 1	o	3	a	
33	28–170	21	M	3	3 yrs.	—	230/160	28 (1 yr.) 119 (4 days)	—	2 (4 days)	420	174	1	50	2 o	—	1	a	
34	32–2024	24	F	8	5 yrs.	—	195/140	200 (2 days)	—	o (6 wks.)	475	210	1—	40	2 o	+	o	a	Exacerbations
35	27–452	24	M	18	18 yrs.	—	158/80	97 (3 wks.)	—	o (3 wks.)	320	135	—	16	o 1—	+	3	a	
36	23–48	25	M	9	9 yrs.	Measles	210/140	165 (4 days)	—	4 (1 mo.)	—	163	—	37	o	+	1	a	
37	17–62	27	F	8	8 yrs.	—	160/? (8 yrs.) 185/100 (2 wks.)	101 (2 wks.)	—	o (2 wks.)	455	150	o	40	1 2	p_v	2	a	
38	19–264	29	M	6	2 mos.	Common cold	170/80	87 (1 mo.)	—	o (1 mo.)	435	340	1	25	1	+	2	b_1	
39	36–2304	29	M	14	1 mo.	Scarlet fever	170/110	27 (1 mo.)	—	o (1 mo.)	540	80 (one)	o	—	1 o	+	o	a	

38	19–264	29	M	6	2 mos.	Common cold	170/80	87 (1 mo.)	—	0 (1 mo.)	435	340	1	25	1	+	2	b_1	
39	36–2304	29	M	14	1 mo.	Scarlet fever	170/110	27 (1 mo.)	—	0 (1 mo.)	540	80 (one)	0	—	1 0	+	0	a	
40	27–261	31	M	3	3 yrs.	Sore throat	180/95 (3 yrs.) 180/90	260 (2 wks.)	—	—	420	175	1—	45	1 0	+	0	a	
41	30–1480	32	F	16	11 yrs.	—	142/82 (11 yrs.) 250/130	50 (1 wk.)	—	60 (10 yrs.) 0 (1 wk.)	350	100	0	75	2	—	0	a	
42	18–117	32	M	10	2 mos.	—	190/140	—	—	0 (2 wks.)	630	405	2	—	2 1	—	2	bd	
43	33–2022	33	M	12	3 mos.	—	220/130	280 (3 days)	—	—	550	180	1	—	1 0	+	0	a	
44	34–267	35	M	16	10 yrs.	Influenza	180/100	—	328 (3 wks.)	—	575	190	0	36	1	+	0	a	Exacerbations
45	27–49	35	F	6	5 yrs.	—	148/90 (3 days)	101 (1 day)	—	—	300	Small	0	30	3	0	2	a	
46	28–1249	36	M	24	5 mos.	—	236/160	152 (6 wks.)	—	0 (7 wks.)	420	90	0	26	3 1	—	1	a	
47	31–1746	37	M	15	12 yrs.	—	220/130	190 (10 days)	—	5 (2 wks.)	680	225	0	39	0	+	1	ad	
48	31–241	38	F	23	16 yrs.	Scarlet fever	225/135	80 (5 days)	—	4 (7 days)	430	220	1	63	1	0	0	ad	
49	35–562	40	M	9	—	—	134/80 (3 days)	279 (1 day)	—	—	546	177	0	36	0	0	2	a	
50	27–653	43	M	6	5.5 yrs.	Sore throat	128/80 (6 yrs.) 260/120 (1 mo.)	15 (6 yrs.) 150 (2 days)	—	—	700	195	1	—	2	p_v	0	a	
51	31–1146	44	F	4	4 yrs.	—	—	65 (5 days)	—	0 (5 days)	350	200	0	—	0 1	—	1	a	
52	37–1993	46	F	15	15 yrs.	—	140/90 (5 yrs.) 215/140 (3 mos.)	31 (5 yrs.) 191 (2 wks.)	—	62 (5 yrs.) 23 (3 mos.)	380	130	—	72	0 1	—	0	ad	Onset during pregnancy
53	33–867	53	F	5	5 yrs.	Common cold	182/106 (1 mo.)	—	163.8 (3 wks.)	—	450	140	0	54	2 0	0	2	a	
54	30–1826	52	M	26	1.5 yrs.	Tonsillitis	238/124	47.6 (6 mos.) 74 (2 days)	—	70 25 (2 mos.)	627	254	0	55	0 1	—	0	b_1	

Explanations as in Table II. P_V = poor vision.

TABLE V

Group III. Subgroup B. Chronic Glomerulonephritis of the Azotemic Type. No History of Acute Glomerulonephritis. Kidneys Weighing Together 250 gm. or More

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Hyaline glomeruli	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%				%		
55	33–1854	8	F	1 yr.	210/120	—	68 (8 days) 156 (1 day)	—	—	80	—	—	0	—	1	20	be	
56	33–855	17	M	8 yrs.	208/130	139 (2 days)	—	—	505	345	—	—	0	+	0	50	be	
57	34–2188	18	F	4 yrs.	140/100 (5 days)	39 (5 days)	—	—	275	300	0	—	1	—	0	40	b_1	
58	25–171	19	M	2 mos.	128/60 (5 days)	—	—	—	360	325	—	—	0	—	1	50	b	
59	22–118	20	F	3 yrs.	190/154	76.6 (6 days)	—	0 (6 days)	420	400	2	70	1 3	+	3	20	b_1	Exacerbations
60	36–2331	21	M	6 mos.+	200/130 (6 mos.) 235/130	—	—	—	525	325	1	—	0	+	0	90	b	Scarlet fever at age of 6 yrs.
61	34–2102	22	F	5 mos.+	—	17.4 (5 mos.)	—	20 (2 mos.)	—	300	0	70	1—	—	0	0	be	
62	35–1131	24	F	1 yr.	164/92	—	222 (3 days)	—	400	350	2	34	1—	—	1	60	b	
63	22–574	29	M	10 mos.	185/125	71 (2 wks.) 142 (2 days)	—	4 (2 wks.)	370	290	0	56	1 0	—	2	20	b_1	
64	14–192	30	M	—	192/?	—	—	—	490	360	—	—	1	—	1—	30	b_1	
65	33–5	30	M	10 yrs.	115/70 (3 yrs.) 170/110	—	176 (4 days)	0 (2 days)	550	400	0	60	0	+	1	70	b	
66	34–356	31	F	4 yrs.	170/90	—	267 (4 days)	—	570	280	1	94	0	+	2	70	b	
67	10–145	32	M	—	—	—	—	—	530	314	3	—	0 2	—	0	10	b_1	
68	15–67	35	F	3 yrs.+	—	—	—	—	400	Normal	0	—	1	—	1	30	b	
69	33–1332	36	M	7 yrs.	130/80	36	—	15	Large	Normal	1	53	1	+	1—	10	b_1	

68	15–67	35	F	3 yrs.+	—	—	—	—	400	Normal	0	—	1	—	1	30	b	
69	27–1200	36	M	7 yrs.	129/80 (1 yr.) 190/120	26 (10 mos.) 178 (3 days)	—	15 (3 days)	Large	Normal	1	53	1	+	1—	10	b_1	
70	17–108	39	M	3 yrs.	—	—	—	0	640	350	0	—	1	p_v	1	50	b_1	
71	19–220	43	M	1 yr.	140/60 (3 wks.)	125 (2 wks.)	—	0 (2 wks.)	Large	300	—	30	0	0	0	5	b_1	
72	11–76	44	F	15 yrs.	170/?	—	—	—	492	260	2	50	2	p_v	1	20	b	
73	33–1906	45	M	20 mos.	255/150	208 (4 days)	—	—	635	264	1—	40	1 3	—	1	60	b	
74	33–933	45	M	1 yr.+	160/120 (2 mos.) 192/140	90 (1 mo.) 245 (2 days)	—	—	380	260	1—	46	0	+	3	60	b	
75	34–1047	45	M	1 yr.+	160/110	40 (6 mos.)	—	—	610	310	1	—	0 3	—	0	50	b	
76	32–1498	47	M	5 yrs.+	224/?	180 (2 days)	—	—	450	360	0	—	1	+	4	40	b	
77	35–1770	48	M	—	High	48 (3 wks.)	87 (2 wks.)	—	400	250	1	—	0	+	3	60	b	
78	32–454	50	M	6 yrs.	225/125	81.9 (3 days)	—	5 (1 mo.)	600	455	2	49	1 3	+	0	15	b_1	Apoplexy
79	33–255	52	M	2.5 yrs.	134/90 (6 mos.)	59.5 (1 mo.)	—	—	519	482	0	—	1	—	3	50	b	Multiple myeloma
80	15–394	54	M	2 mos.	168/90	—	—	—	650	319	0	—	1 0	—	0	60	b	Old valve defect
81	36–2169	56	F	—	185/90	131 (5 days)	—	—	350	250	1	94	0	+	4	30	b_1d	
82	22–176	56	M	10 yrs.	184/100	—	—	—	500	475	1—	—	1	0	0	10	b_1	
83	31–465	60	F	9 mos.	220/120	44.5 (2 mos.)	—	—	427	312	0	50	1	—	2	30	bd	Diabetes
84	36–552	60	M	3 mos.	140/70 (3 mos.)	38.5 (6 wks.)	—	—	495	280	3	—	0 2	0	1	20	b_1	
85	16–119	63	M	—	—	—	—	—	400	300	0	—	0	—	3	30	b_1	
86	30–209	65	M	2 yrs.	156/82	79 (9 days) 167 (2 days)	—	10 (9 days)	500	250	0	68	0	—	3	50	b_1	
87	29–869	68	F	—	210/?	—	—	—	500	300	1	—	2	—	1	50	b_1d	Diabetes

Explanations as in Table II. Explanations of histological types in the text.

TABLE VI

Group III. Subgroup C. Chronic Glomerulonephritis of the Azotemic Type. Kidneys Weighing Together Less than 250 gm.

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%	*gm.*	*gm.*		%					
88	30–519	14	F	1 yr.+	–	176 (3 wks.)	–	–	170	185	o	43	1–	–	2	b_1	
89	15–373	23	M	3 mos.	180/115	–	–	11 (2 mos.)	557	Small	–	50	1	–	o	a	
90	16–384	24	M	3 mos.	170/90	131 (5 days)	–	o (6 days)	415	205	o	20	1	–	2	b_1	
91	33–214	24	M	1 mo.	188/90	296 (1 day)	–	–	400	87	o	20	1	–	3	a	
92	32–947	25	M	—	150/70	240 (1 day)	–	–	380	140	o	54	o	–	o	a	
93	37–1501	25	M	6 wks.+	168/98	120	–	o (2 wks.)	450	122	–	36	1	o	o	a	
94	27–1287	25	M	3 mos.	220/160	82 (2 wks.) 116 (1 day)	–	16 (2 wks.)	325	105	o	65	2	ed	o	a	
95	19–2	25	M	9 mos.	210/118	72 (9 days)	–	o (9 days)	500	195	–	–	o	+	1–	a	
96	26–286	26	F	4 yrs.	160/110 (3 yrs.) 210/130 (1 yr.)	72 (3 yrs.)	–	–	380	210	2	–	1 o	o	1	b_1	Exacerbations
97	22–47	27	M	2.5 yrs.	182/110	133	–	o	540	110	o	30	1 o	–	2	a	
98	24–697	27	M	–	122/44 (1 day)	–	–	–	200	52	o	–	o	–	o	a_1	
99	32–1935	27	M	10 yrs.	194/114	131 (3 wks.) 216 (3 days)	–	–	550	175	1–	–	o	+	4	a	

100	16–132	27	M	3 mos.	–	–	–	–	425	150	0	36	1	–	2	a	
101	36–12	28	M	7 yrs.	154/100 (9 mos.)	140 (5 days)	–	0 (5 days)	350	71	0	59	0	–	0	a	
102	36–1467	28	F	6 yrs.	185/80	–	–	–	325	50	1–	–	1 0	+	1	a	
103	28–1446	29	F	2 yrs.	114/94 (2 yrs.) 194/124	124	–	–	430	80	–	60	1–	–	2	a_1	
104	37–2199	29	F	10 yrs.	172/102 (2 yrs.) 190/110	80 (3 mos.) 203	–	–	425	113	–	36	1	+	0	a	
105	15–363	30	M	3 yrs.	–	–	–	0 (1 mo.)	575	155	–	–	0 3	–	1	a	
106	31–1247	31	F	5 yrs.+	190/110	–	–	–	275	95	0	–	1	–	0	a	Exacerbations
107	32–2089	32	F	–	130/60 (3 days)	–	214 (1 day)	–	–	50	–	–	1–	–	0	a	
108	34–673	32	F	4 yrs.	180/110 (2 yrs.) 230/160	48 (14 mos.) 157 (2 days)	–	–	518	81	0	35	0 2	+	2	a	
109	19–160	32	M	–	120/80 (3 days)	–	–	–	350	140	0	–	0	–	2	a	
110	28–1189	33	F	6 yrs.	210/?	60 (2 wks.)	–	–	350	120	0	45	0	–	2	a	
111	22–128	33	F	9 yrs.	154/92	29.6 (2 wks.)	–	–	360	230	0	70	1	–	0	b_1	
112	32–2005	34	M	3 yrs.+	180/120	60 (2 mos.)	184 (2 mos.)	4 (2 mos.)	360	95	0	–	0 1	+	4	a	
113	20–204	34	M	3 mos.	200/120	–	–	–	425	195	1–	–	1–	+	2	a	
114	13–145	35	M	4 mos.	132/? (4 mos.)	–	–	–	475	169	0	35	2	–	2	a	
115	23–267	35	F	9 mos.	140/90 (11 days)	–	–	0 (8 days)	375	135	2	–	2	–	3	a	

TABLE VI (*Continued*)

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Weight of heart	Weight of kidneys	Passive congestion of liver	Hemoglobin	Edema	Retinitis	Epithelial crescents	Histological type	Comment
		yrs.			*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	*%*	*gm.*	*gm.*		*%*					
116	23–293	35	M	4 yrs.	142/100 (4 yrs.) 202/132	120 (2 days)	—	0 (3 wks.)	500	123	—	38	1 0	—	0	a	
117	26–251	35	F	—	250/160	169 (1 day)	—	—	370	200	1	67	0	+	1	ad	Diabetes
118	31–1197	37	F	3.5 yrs.	158/98 (3 yrs.) 200/120	Normal (3 yrs.) 110 (7 mos.)	—	40 (3 mos.)	350	140	0	74	0	e_d	0	a	
119	28–734	37	M	1 yr.	160/130	132 (6 days)	—	0 (6 days)	450	200	1	64	0	+	0	a	
120	35–360	37	F	7 yrs.	275/150	31.5 (2 yrs.) 119.7 (1 day)	—	—	544	155	0	47	2 1—	p_v	0	b	
121	28–347	39	F	—	—	37.8 (6 mos.)	—	—	370	226	1	55	1	—	3	b	
122	37–1290	40	M	—	—	62 (1 day)	132 (1 day)	—	300	60	0	—	0	—	0	a	
123	31–1063	40	F	4 yrs.	240/150	155 (2 mos.)	—	53 (2 yrs.) 1 (2 mos.)	520	140	—	44	2	—	2	a	
124	37–643	40	M	2 yrs.+	200/145	—	—	—	600	185	1	50	0	+	0	a	
125	30–1631	41	M	3 yrs.	220/150	—	90 (8 mos.)	—	550	210	—	—	2 0	+	1	a	
126	21–434	41	F	1 yr.	180/70	238 (6 days)	—	0 (11 days)	560	150	1—	—	2 1	p_v	1—	a	
127	23–604	41	F	7 mos.	210/140	196 (10 days)	—	10 (3 wks.)	385	110	1—	48	3 1	p_v	0	a	

128	23–635	41	F	4 yrs.	134/90 (3 yrs.) 185/130	34 (2 yrs.) 185 (2 days)	—	10 (2 yrs.) 0 (2 days)	365	63	0	54	0 1—	—	2	a	
129	22–619	46	F	9 wks.	120/88 (3 wks.)	56 (10 days)	—	10 (10 days)	380	165	0	44	2 0	—	4	a	
130	17–207	46	F	11 yrs.+	160/110 (3 days)	89 (3 days)	—	0 (3 days)	400	120	—	50	0 2	—	2	a	Exacerbations
131	28–1369	47	M	5 yrs.	110/70 (12 hrs.)	121.8 (1 day)	—	—	355	140	0	45	0	—	2	a	
132	32–1453	48	M	—	High	—	—	—	450	112	1—	55	0	—	1	a	
133	36–715	49	M	1 yr.	—	—	230 (2 wks.)	0 (2 wks.)	510	110	3	38	0	—	0	a	
134	18–94	50	M	6 yrs.	188/124	—	—	—	640	205	—	75	1	—	2	a	
135	34–2030	52	M	1 yr.	200/135	—	83.7 (1 yr.) 227 (12 days)	5 (3 wks.)	500	185	0	32	0	0	1	a	
136	26–459	56	M	—	180/100	—	—	—	400	135	0	28	1—	—	2	a	
137	30–473	62	M	1 yr.	194/110	82.6 (3 wks.) 183 (1 wk.)	—	1 (9 days)	450	200	0	—	1	—	1	a	
138	31–1817	62	F	2 yrs.	Normal	85 (5 mos.) 100 (6 wks.)	—	—	275	150	0	—	1	—	0	a	
139	17–73	65	F	8 yrs.	200/95	156 (1 day)	—	23 (3 yrs.) 10	435	190	—	50	0 2	+	3	ad	
140	21–437	71	M	—	192/64	—	—	—	625	210	—	—	1	—	0	a	Old valve defect
141	15–139	72	M	3 mos.	—	—	—	—	686	223	—	—	1	—	4	a	

Explanations as in Table II. Explanation of histological types in the text.

The symptoms in the active chronic stage vary in intensity in the different patients.

In 7 cases there was a history of repeated acute exacerbations during which all the symptoms, including edema, albuminuria and decreased renal function became more intense. After the subsidence of the acute exacerbations the symptoms return to their previous levels, but there is a tendency to progressive impairment of renal function. The active chronic stage is therefore characterized either by continuous symptoms of low intensity or by acute exacerbations separated by intervals of varying length during which the symptoms are of only moderate severity.

The Blood Pressure: In the tables the maximum blood pressure is recorded and this pertains to the terminal stages of the disease unless otherwise stated. In a few instances a blood pressure taken some months or years before death is recorded, the time prior to death being indicated in the table. There are 9 cases in which the maximum systolic blood pressure recorded was below 140 mm. Hg., *viz.*, Cases 49, 58, 79, 98, 107, 109, 114, 129 and 131. It is unlikely, however, that all of these cases represent chronic glomerulonephritis without hypertension. In Cases 49, 79 and 114 the marked enlargement of the heart is strong evidence that hypertension was present at some previous period, and in Cases 58, 98, 107, 109 and 131 the blood pressure was not recorded until shortly before death, a period during which terminal circulatory failure often develops. The period of observation in all of these cases is too short to justify the diagnosis of "chronic glomerulonephritis without hypertension." However, the small size of the heart in Cases 57, 98 and 138 suggests that hypertension did not play an important rôle in these instances. Cases have also been reported in which there was no elevation of blood pressure during a long period of observation (Bannick [4]).

In 88 cases with a maximum systolic pressure of 150 mm. Hg. or higher the distribution was as follows: 150 to 170 mm. Hg., 12 cases; 170 to 200 mm. Hg., 39 cases; over 200 mm. Hg., 37 cases. The large proportion of cases (30 per cent) with a systolic pressure above 200 mm. Hg. is surprising. In one instance a pressure of 275 mm. Hg. was recorded. This is conclusive evidence that a blood pressure above 200 mm. Hg. is not evidence against a diagnosis of chronic glomerulonephritis as is sometimes supposed.

The blood pressure usually tends to rise to higher levels as the renal disease progresses (note Cases 26, 41, 50, 52, 65, 69, 96, 103, 116, 118 and 128). Over a period of years it rises gradually to a maximum and usually does not decrease until a short time before death. The blood pressure rises as renal insufficiency increases. This phenomenon is in striking contrast with primary hypertension in which high levels of blood pressure are attained early in the disease.

The Weight of the Heart: The weight of the heart in 111 cases is as follows: 200 to 300 gm., 4 cases; 300 to 400 gm., 30 cases; 400 to 500 gm., 35 cases; 500 to 600 gm, 28 cases; and 600 to 700 gm., 13 cases. The average weight of 110 hearts is 456 gm. The hypertrophy in all instances is of left ventricular type. There is no obvious explanation of the great variation in the size of the heart. Apparently the weight of the heart is not directly related to the duration of the disease nor to the height of the recorded blood pressure. Perhaps we should not expect to find such a correlation since the work required of the left ventricle must depend upon the constancy as well as the degree of hypertension and the length of time involved. It often happens that the blood pressure is only moderately elevated for a number of years and becomes very high only in the terminal stages.

There is some relation between the size of the heart and the age of the patient. In 68 individuals under 40 years of age the average weight of the heart is 438 gm., while in 42 individuals over 40 years of age the average weight is 484 gm. Hearts weighing 500 gm. or more were found in 20 of 68 persons under 40 years of age (30 per cent), and in 20 of 42 over 40 years of age (48 per cent).

The average weight of 68 hearts from males is 489 gm., and of 42 hearts from females 403 gm. The normal heart averages about 50 gm. heavier in males than in females.

Judged by passive congestion of the liver there is some degree of heart failure in nearly one-half of the cases. As shown in Tables IV, V and VI, in 93 cases in which the liver was examined microscopically there were 51 cases with no passive congestion (0), 13 with very slight congestion (1–), 17 with definite but slight central atrophy (1), 9 with some central necrosis (2), and 3 with severe central necrosis (3) such as one finds in death from chronic myocardial failure.

In 1 of the 3 cases with severe passive congestion of the liver (Case 133) a high degree of renal insufficiency was established clinically and in the other 2 an anatomical diagnosis of uremia is justifiable. In 7 of the 9 cases with Grade 2 passive congestion of the liver, uremia was established clinically. We may conclude that heart failure of an appreciable degree may develop in chronic glomerulonephritis and that it may be exceptionally an important contributory cause of death, but uremia is practically always present at the time of death.

In striking contrast with primary hypertension a history of stroke was obtained in only 1 of the 117 patients (Case 78). There was only one typical example of coronary disease (Case 87, a woman 68 yrs. old). In 10 other cases there was complaint of precordial pain at times, but no severe coronary disease was found at postmortem.

Renal Function: It is noteworthy that the blood urea nitrogen seldom rises to high levels until a few weeks before death. Determinations made 6 months or more before death usually range from 25 to 50 mg. per cent. A very marked increase usually takes place during the last 1 or 2 days, and a striking increase is noted during the last 1 or 2 weeks. After the blood urea nitrogen has reached a level of 100 mg. per cent the patient seldom survives more than a few weeks. The marked variations in the terminal level of blood urea in different individuals may be due in part to differences in the amount of protein consumed. It is clear that extreme reduction of the number of functioning nephrons has usually taken place before the blood urea nitrogen rises above 40 mg. per cent. There is commonly a slowly progressive rise of blood urea until the terminal stages when a rapid increase occurs, but occasionally a patient will exhibit a marked elevation, due to an acute exacerbation of the nephritis, which returns to the previous level after the acute process has subsided.

Wakefield and Keith [5] reported a patient with a blood urea of 290 mg. per cent and a phenolsulphonephthalein output of 0, who recovered and was working in comfort 1 year later.

The phenolsulphonephthalein test gives about the same information as the determination of blood urea. With few exceptions the two tests run parallel, and the only advantage of doing both is the avoidance of possible errors.

Anemia: A hypochromic anemia of fairly severe degree is present in the terminal stages in the great majority of cases. The hemoglobin percentage was 50 or less in over two-thirds of the cases in which it was determined. In only 2 cases was there no anemia. In general the severity of the anemia increases as renal function decreases.

Retinitis: Retinitis, in the sense of retinal hemorrhages and exudates, was observed in 35 of the 46 cases in which the eyegrounds were examined (Table VII) and it was noted in 7 other cases that the patient had poor vision. The data on the caliber of the retinal arteries is too inadequate for discussion. It is well

TABLE VII

The Relation between Retinitis and the Level of the Systolic Blood Pressure. (The Eyegrounds Were Examined in Only 46 of the 103 Cases)

Blood pressure. Systolic mm. Hg.	Number	Retinitis +	Retinitis —
Below 140.....	8	0	1
140–150.....	7	0	3
150–170.....	12	2	2
170–200.....	39	16	2
Above 200	37	17	3
	103	35	11

recognized that retinitis is a result of hypertension. In Table VII it appears that retinitis was present in 33 of 38 patients with a systolic pressure above 170 mm. Hg. In the stage of uremia, primary hypertension and chronic glomerulonephritis usually cannot be distinguished by the appearance of the eyegrounds.

Edema: It is impossible to give a true picture of the degree and duration of edema by means of a summarizing table. In Tables IV, V and VI the numerals give only a rough estimate of the degree of edema during the period of observation. Edema is usually much more marked during acute exacerbations, and it varies greatly in intensity from time to time during the active chronic stage. It was not continuously severe in any of the cases in Group III (Cases 25 to 141). The cases in which edema was a constant and prominent feature are listed in Tables VII, VIII and IX. In 31 patients there was no edema at any time during the period of observation. Edema is often present early in the disease and absent in the

terminal stages, but frequently it is present only toward the end of the illness.

Edema is dependent upon several factors, the most important of which is probably the level of the plasma proteins, but the data in our records are inadequate for a discussion of this relationship. There is no evident relation between edema and the degree of contraction of the kidneys in Group III. Presumably increased venous pressure resulting from myocardial failure is often a factor of importance, but if passive congestion of the liver is taken as evidence of cardiac decompensation it may readily be seen from the tables that there is no close correspondence between edema and cardiac failure. However, there is a possible correlation between terminal edema and passive congestion of the liver. Congestion of the liver was present in 11 of 45 cases without terminal edema and in 18 of 49 cases with terminal edema.

The Relation between the Size of the Kidneys and the Clinical Features: For purposes of comparison the cases without a history of acute onset have been arranged in two groups, *viz.*, those with kidneys weighing 250 gm. or more (Table V), and those with definitely contracted kidneys weighing from 50 to 250 gm. (Table VI). The weights of the kidneys in the group with a history of acute onset (Table IV) may also be compared. It appears from these tables that it is not possible to predict the size of the kidneys from a study of the clinical history. One might expect that the cases of longer duration would show the greater degree of contraction of the kidneys, but this relationship does not obtain as may be seen by a study of Table IV. There is likewise no evident relation between the degree of contraction of the kidneys and the size of the heart, the level of the blood pressure or the prominence of edema. However, when edema is continuously severe, as in Group IV, one may predict that the kidneys will not be contracted.

The size of the kidneys in the azotemic and hydropic types is shown in Chart 1. It appears that the azotemic kidneys are usually much smaller than the hydropic but that some overlapping occurs. In the azotemic type (Group III) the combined weight of the kidneys is as follows: 50 to 99 gm., 13 cases, 11.5 per cent; 100 to 149 gm., 22 cases, 19.5 per cent; 150 to 199 gm., 26 cases, 23 per cent; 200 to 249 gm., 17 cases, 15 per cent; 250 to 299 gm., 10 cases, 8.8 per cent; 300 to 349 gm., 13 cases, 11.5 per cent;

350 to 399 gm., 4 cases, 3.5 per cent; 400 to 449 gm., 3 cases, 2.6 per cent; and 450 to 500 gm., 4 cases, 3.5 per cent. In the hydropic type (Group IV) the kidneys weighed over 300 gm. in 22 of 38 cases, as may be seen in Chart 1. In the azotemic group, in which uremia was always present at death, it may seem remarkable that uremia should develop in some instances when the kidneys are still of normal size and in others not until their weight is less than 100 gm., but these differences are explainable on the basis of the histological structure of the kidneys.

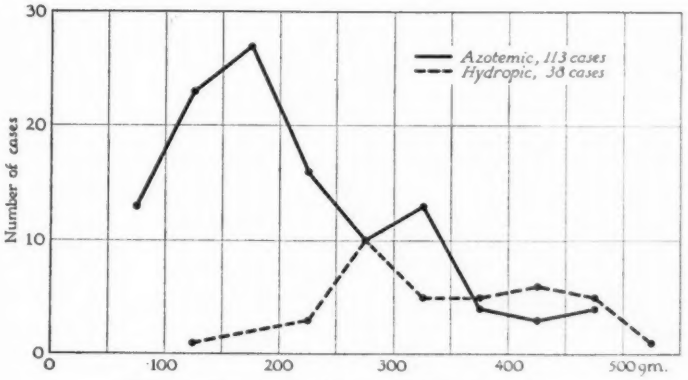

Chart 1. Size of the kidneys in azotemic and in hydropic glomerulonephritis.

The Structural Changes in the Kidneys

The variations in the size of the kidneys in the terminal stages of chronic glomerulonephritis are related to the structural changes that have taken place. These changes may be described as histological types and are so indicated in Tables IV, V and VI. From a study of the histological structure it may be determined why some kidneys are much smaller than others when the stage of uremia is reached.

As a result of acute glomerulitis the glomerular capillaries show a variety of effects ranging from no obstruction at all to complete obliteration. When the capillaries are normal, or only slightly narrowed, glomerular filtration continues and the tubules are unaffected, but when the capillaries are completely closed the glomerulus becomes hyaline and the tubules disappear entirely or

become small epithelial cords. Intermediate degrees of capillary obliteration, however, result in partial but not complete suppression of glomerular function and the associated tubule shows a degree of atrophy corresponding to the state of its glomerulus. Damaged glomeruli with partial tubular atrophy are a prominent feature of many kidneys (Fig. 6). When a large proportion of the glomeruli are of this type the kidneys may reach the stage of renal insufficiency without having undergone contraction. The varying sizes of the kidneys in the stage of uremia depend largely upon the proportion of glomeruli with partial tubular atrophy. In order to condense the histological descriptions the histological type of each kidney is given in the table. These types will be described and illustrated.

1. *Type a:* This is the most common form of chronic glomerulonephritis. The kidneys are small and contracted, the combined weight is usually less than 200 gm. and never over 250 gm. Sometimes they are extremely small (Cases 102, 107, 122 and 128). The cortices are thin. In microscopic sections (Fig. 5) it is noted that a large majority of the glomeruli are hyaline and that the tubules associated with these glomeruli have almost completely disappeared. A differential count usually shows that 80 to 90 per cent of the visible glomeruli are hyaline. The amount of destruction of the cortex is probably even greater than 80 or 90 per cent, since it is known that many hyaline glomeruli are ultimately removed by phagocytes (Moritz and Hayman [6]). Of the persistent glomeruli a few are normal with full sized tubules and some are partially obstructed with tubules showing corresponding stages of atrophy. The proportion of normal to partially obstructed glomeruli varies in different kidneys, sometimes the one predominating, sometimes the other.

Type a_1: This subgroup of Type *a* is represented by only 2 cases (Cases 98 and 103). In both of these the kidneys were very small but only a few hyaline glomeruli were to be seen. It is assumed that in these cases the hyaline glomeruli have been absorbed. One of these (Case 98) was a dwarf, weighing 80 pounds, and it is conceivable that this represents primary hypoplasia rather than atrophy.

Type a_2: This is represented by only 1 case (Case 28). There is a terminal acute glomerulonephritis superimposed on a chronic

glomerulonephritis. The persistent glomeruli show fresh epithelial crescents and other acute changes.

Type ad refers to Type *a* with an associated arteriolosclerosis. There are 8 cases with arteriolosclerosis (Types *ad* and *bd*) and all are characterized by very high blood pressure. The arteriolosclerosis is diffuse and severe. It is not uncommon to find an occasional hyaline arteriole in this disease but severe arteriolosclerosis is unusual.

Many investigators have apparently confused atrophy of small arteries and arterioles with true arteriolosclerosis. Segments of the cortex which contain nothing but hyaline glomeruli and atrophic tubules are functionless and require no blood. The arteries and arterioles supplying such scar-like areas undergo a disuse atrophy which may readily be confused with arteriolosclerosis, but the change is chiefly medial fibrosis and not intimal disease. Arteriolar disease, apart from atrophy, is so rare in chronic glomerulonephritis that it may be an accidental relationship. The structural changes in the arterioles in chronic glomerulonephritis do not support the argument that hypertension causes arteriolosclerosis.

2. *Type b* (*Fig. 6*): In this group the kidneys may show a slight reduction in size, a normal weight or even an enlargement. The size of the kidneys is not directly related to the duration of the disease. On microscopic examination it is found that the hyaline forms constitute less than one-half of the visible glomeruli. Frequently only 10 to 20 per cent of the glomeruli are hyaline, and rarely no hyaline glomeruli are to be seen. The most frequent type of nephron in these large kidneys is a damaged glomerulus with moderate atrophy of its tubule. With this type of lesion there is not much shrinkage of the renal cortex.

Type b_1 is a subgroup of Type *b* in which there are few or no normal glomeruli and tubules, the great majority of the nephrons being partially obstructed glomeruli with varying degrees of tubular atrophy (Fig. 7).

Type bd refers to Type *b* with an associated arteriolosclerosis; and Type *be* indicates Type *b* with extensive thrombosis of arterioles. There are 3 cases with widespread acute thrombosis of arterioles.

It is evident from the foregoing descriptions that small kidneys are those in which a large proportion of the nephrons have under-

gone complete atrophy because of complete closure of all the glomerular capillaries. In the small kidneys there are nearly always a few normal glomeruli with normal sized or hypertrophic tubules, and there are usually some partially closed glomeruli with tubules of diminished size. In the large kidneys normal and injured glomeruli outnumber the hyaline forms. Damaged glomeruli have a reduced functional capacity and one normal glomerulus is probably equivalent functionally to several injured forms. In a few instances nearly all the functioning glomeruli are of the damaged type (Type b_1). Uremia evidently may develop, as it does in the subacute type, before a large proportion of the glomeruli have become hyaline.

It is unlikely that the complex structure of the kidney seen at postmortem is the result of a single acute attack. In acute glomerulonephritis the intensity of the injury varies in different glomeruli — some escape with only minor injury, others suffer occlusion of a part of the glomerular circulation, and some exhibit complete capillary occlusion. In the healing stage after such an acute attack we would expect to see some normal glomeruli and tubules, some partially obstructed glomeruli with moderate atrophy of their tubules, and some hyaline glomeruli with disappearance of tubules. After the acute stage has subsided we would expect renal function to continue at a constant but reduced level. It is probable that repeated reinfections are responsible for the progressive failure of renal function in chronic nephritis.

Group IV. Chronic Glomerulonephritis of the Hydropic Type

In all the cases of this group edema was present during the greater part of the course of the disease and usually it was a very prominent feature. There were often one or more acute exacerbations during which albuminuria and edema were very severe, and remissions during which these features were much less intense. From the clinical standpoint all three subgroups of Group IV may be regarded as lipoid nephrosis in the sense in which this term is now generally used. There are no clinical features by which the three subgroups may be distinguished from one another, but there are histological differences in the structure of the glomeruli.

Subgroup A (Table VIII): In this group there are 6 cases that

TABLE VIII

Group IV. Subgroup A. Hydropic Type. Glomerular Structure of Proliferative Type

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%			
142	37–524	16	F	14 mos.	4	4	145/90	15.4		44		4.54	498	340	46	0	10	1p	0	Hydro-
							(1 yr.)	25.2	—	(1 yr.)	—	(1 yr.)								thorax
							220/150	(1 mo.)		12		1.76								
										(1 wk.)		(1 mo.)								
143	34–2212	21	F	9 mos.	1	4	140/86	22.4	—	17	—	—	358	402	50	—	0	0	0	Parotitis
					2		(4 mos.)	(3 wks.)		(2 wks.)										
							120/70													
							(3 wks.)													
144	34–1543	41	M	7 yrs.	4	4	190/130	—	—	—	—	—	325	435	—	0	10	1p	0	Hydrotho-
																				rax and
																				ascites
145	24–580	68	M	4 mos.	2	3	200/115	41.5	—	—	—	—	350	275	—	1	0	0	1p	Lobar
					4			(1 mo.)												pneumonia
146	28–906	37	F	3.5 yrs.	3	1	142/104	38.5	—	—	—	—	340	136	54	3	50	2	2p	Mitral
						4	162/114	(3 mos.)												stenosis
147	34–633	76	F	3 mos.	1	4	—	—	—	—	—	—	375	240	20	1—	0	0	2p	Severe
																				anemia

correspond clinically to lipoid nephrosis but belong anatomically with proliferative glomerulonephritis. A representative case of this group is reported fully:

CASE 142. *Clinical History:* A white female, 16 years old, was first admitted to the hospital Jan. 25, 1936. On Dec. 24, 1935, she had had several short attacks of pain in the right upper quadrant associated with flatulence and belching. During the next few days there were repeated attacks of vomiting but no pain. About Jan. 2, 1936, she first noticed swelling of the face, feet and ankles. The edema disappeared after a few days in bed. She had had scarlet fever about 1 year before the onset of the present illness and an occasional attack of sore throat during the previous 2 years.

On admission, Jan. 25, 1936, there was a marked edema of the face and the extremities. The systolic blood pressure was 145 and the diastolic 90 mm. Hg. Rales were heard in the bases of both lungs. The fundi were normal. Repeated examinations of the urine showed a specific gravity from 1017 to 1031, albumin ++++, and many casts and erythrocytes in all specimens. The 24 hour diuresis varied from 200 cc. to 1700 cc., being usually about 700 cc. The fluid intake was about 1200 cc.

The hemoglobin fell from 66 per cent on admission to 46 per cent shortly before death, and the erythrocytes from 3,660,000 to 1,800,000. The 2-hour excretion of phenolsulphonephthalein was 44 per cent (February 1936), 12 per cent (March 1936), and 26 per cent (October 1936). The blood urea nitrogen varied from 15.4 to 25.2 mg. per cent, creatinin from 1.5 to 2 mg. per cent. The total plasma proteins were 4.54 gm. per cent (April 1936), 6.27 gm. (May 1936) and 1.76 gm. (February 4, 1937).

The blood pressure varied from 145/90 on admission to 220/150 in November 1936. The edema varied in intensity from time to time but was usually quite pronounced. Dyspnea was usually a prominent symptom and headache was often severe. Death occurred on March 3, 1937. The clinical diagnosis was lipoid nephrosis.

At postmortem there was extreme anasarca. The peritoneal cavity contained about 1000 cc. of clear fluid, the right pleural cavity 500 cc., the left pleural cavity 800 cc., and the pericardial cavity 300 cc. There was also marked edema of the lungs. Death was apparently due largely to edema of the lungs and hydrothorax.

The heart weighed 498 gm. and showed left ventricular hypertrophy. There was no passive congestion of the liver.

The kidneys weighed 340 gm. and showed smooth external surfaces. On section a yellowish tinge was noted. On microscopic examination only an occasional hyaline glomerulus is noted, and there is a very little patchy tubular atrophy. All the glomeruli are moderately enlarged and uniformly involved. Lobulation is distinct. The lobules show central masses of hyaline of varying amount, formed by thickening and fusion of the centrally placed

capillary basement membranes (Fig. 8). The glomerular structure corresponds entirely to that of chronic proliferative glomerulonephritis, but death occurred from edema before any appreciable atrophy of parenchyma had taken place. The structure is therefore quite different from that of the great majority of cases in which death is due to uremia and the kidneys are atrophic. There is no diffuse thickening of the capillary basement membranes which characterizes most cases of lipoid nephrosis.

The other 5 cases of Subgroup A are similarly examples of chronic proliferative glomerulonephritis in which death occurred in a comparatively early stage of the disease. It may be said therefore that chronic proliferative glomerulonephritis may in unusual instances completely reproduce the clinical syndrome which we are accustomed to call "lipoid nephrosis."

Subgroup B (Table IX): This group includes 9 cases in which the clinical diagnosis was lipoid nephrosis. On the basis of the data presented a few of these cases may be considered examples of pure lipoid nephrosis in the broad sense but there was in most instances a little hypertension, some azotemia or a reduced output of phenolsulphonephthalein. There was only one death from uremia. In one instance, Case 156, edema was not very prominent and the case was classified in this group because of the thick capillary basement membranes. In Case 148 there was marked cardiac hypertrophy and hypertension. The plasma proteins were very low in the 2 cases in which they were determined, Cases 149 and 150. There is no evidence in any case that edema was of cardiac origin.

The most interesting feature of this group is the glomerular lesion. In only one instance, Case 148, is there any large proportion of hyaline glomeruli, and in 2 cases there are none. Aside from the hyaline forms the glomeruli are nearly all large with many permeable capillaries.

The glomerular lesions are partly of membranous and partly of proliferative type. In Cases 150 and 156 the glomeruli resemble those shown in Figures 2 and 3 except that the basement membranes are much thicker. Case 154 differs from these only in the presence of many fresh epithelial crescents. Case 149 is a typical membranous type except for a few glomeruli of the proliferative form. Cases 148, 151, 152, 153 and 155 show only occasional

TABLE IX

Group IV. Subgroup B. Hydropic Type. Thick Basement Membranes, but many Glomeruli of Proliferative Type

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%			
148	35–1222	24	F	17 mos.	3	3	194/130 (2 days)	—	87.6 (2 days)	—	—	—	550	230	48	—	70	3	4	Hydrothorax
149	37–271	27	F	4 mos.	3	2 1	136/80 (2 mos.)	—	12.6 (2 mos.) 46 (2 wks.)	70 (2 wks.)	—	4.2	310	475	42	0	5	0	4	Lobar pneumonia
150	29–1880	27	M	3 yrs.	3	3	160/100	9 (1 mo.)	36 (1 mo.)	65 (1 mo.)	—	a, 0.69 g, 3.26	—	—	74	0	10	1—	3	Peritonitis
151	31–1672	37	M	16 mos.+	3	3	150/90	—	—	—	—	—	325	435	—	0	5	0	3	Hydrothorax and ascites
152	20–43	38	M	5 yrs.	3	3	122/84 (1 mo.)	16.4 (1 mo.)	—	30 (1 mo.)	—	—	325	390	52	0	10	1—	2	Pneumonia
153	27–925	39	F	8 yrs.	—	2 4	—	—	—	—	—	—	264	267	20	0	0	0	2	Severe anemia
154	17–230	45	M	1 yr.	2	1 4	140/70	24 (9 days)	—	30 (1 mo.)	—	—	400	360	—	0	0	2	2	Lobar pneumonia
155	33–574	45	M	—	4	4 0	128/70 165/80 (3 wks.)	22 (3 wks.)	42 (3 wks.)	65 (3 wks.)	—	—	425	400	—	0	10	1—	3	
156	27–305	52	F	2 yrs.	+	1	—	—	—	—	—	—	315	350	80	0	10	1	3	Peritonitis from perforated ulcer

Under plasma proteins, a = albumin, g = globulin.

glomerular lobules of proliferative type, all the others being membranous.

The glomerular structure in Subgroup B is therefore a blending of proliferative and membranous lesions with a predominance of the latter. There is a much closer resemblance to lipoid nephrosis than to azotemic glomerulonephritis.

Subgroup C (Table X): In the 25 cases in this group the clinical diagnosis was lipoid nephrosis and the glomeruli show no evidence of proliferative glomerulitis. Six of the 25 cases show no visible alterations in the glomeruli. It is certain that these 6 cases correspond to what others have called pure nephrosis but none of them satisfies the arbitrary definition laid down by Leiter that there shall be no elevation of blood pressure or decrease in renal function. However, they satisfy the criteria suggested by Blackman in that there is no progressive hypertension or renal insufficiency. Clinically there are no distinctions between those with no changes in the basement membranes (Cases 157, 158, 159, 160, 162 and 163), those with patchy membrane thickening (Cases 161, 164, 165 and 173) and 2 of those with pronounced thickening of the basement membranes (Cases 166 and 167). The great majority of those with thick basement membranes show hypertension.

It is noteworthy that in the 11 children (Cases 157 to 167) the structural changes in the glomeruli were much less pronounced than in the adults. Thirteen of the 14 adults but only 2 of the 11 children showed a diffuse thickening of the basement membranes.

The plasma proteins were markedly reduced in 12 of the 13 cases in which they were determined. Cardiac failure plays no rôle in causing edema since passive congestion of the liver was present only in the 1 case with death from endocarditis.

There were 4 deaths from uremia and 17 from infectious processes. Twelve of the 17 infections were peritonitis, of which 5 were streptococcic, 2 pneumococcic and the others undetermined. An incomplete survey of the literature shows that peritonitis was assigned as the cause of death in 42 of 53 cases. Of these, 23 were pneumococcus infections, 10 streptococcic and 9 not specified.

The clinical course of the disease was usually characterized by alternating exacerbations and remissions, the symptoms being intense during the former and mild during the latter. In Case 159

TABLE X

Group IV. Subgroup C. Hydropic Type without Proliferative Glomerulitis. Thickened or Normal Capillary Basement Membranes

Case No.	Autopsy No.	Age	Sex	Duration of symptoms	Albuminuria	Edema	Blood pressure	Urea nitrogen	Non-protein nitrogen	Phenolsulphonephthalein	Cholesterol	Plasma proteins	Weight of heart	Weight of kidneys	Hemoglobin	Passive congestion of liver	Hyaline glomeruli	Tubular atrophy	Basement membrane	Cause of death	Comment
		yrs.					*mm. Hg.*	*mg./100 cc.*	*mg./100 cc.*	%		*gm. %*	*gm.*	*gm.*	%		%				
157	34–383	1.5	M	6 wks.	4	3	114/70	—	—	—	—	—	—	300	—	0	0	0	0	Peritonitis	
158	31–886	3	F	7 mos.	4	4	90/50	31.5 (6 mos.) 10.7 (2 mos.)	—	33 (2 mos.)	240	—	65	190	50	0	0	0	0	Pneumococcic peritonitis	Onset with sore throat
159	35–461	4	M	16 mos.	4	4 0	110/68	21 (1 yr.) 58 (p. m.)	—	—	251	a, 1.07 g, 5.97 f, 0.8	75	250	82	0	0	0	0	Str. viridans peritonitis	Repeated attacks of peritonitis
160	35–242	5	F	15 mos.	1 4	3	94/68	13 (1 yr.)	71 (1 day)	—	244	a, 2.0 g, 2.2 f, 0.8	—	250	75	0	0	0	0	Peritonitis	Followed a cold
161	33–1579	5	M	2.5 yrs.	1 4	4	95/60 110/70	10.5 (1 mo.)	45 (1 mo.) 27.6 (3 wks.)	30 (1 mo.)	215	a, 1.65 g, 2.11	75	290	70	0	5	1p	3p	Streptococcic peritonitis	Followed pneumonia
162	26–625	6	F	6 mos.	3	4	—	27 (6 wks.) 19 (1 mo.)	—	15 (2 wks.)	—	—	60	275	68	—	5	1p	0	Peritonitis	
163	33–1472	7	M	13 mos.	4	3	96/66	11.7 (9 mos.) 29 (1 day)	45.8 (10 mos.) 75.8 (1 day)	40 (9 mos.) 74 (1 mo.)	—	a, 1.8 g, 2.8 f, 0.4	290	267	—	0	0	0	0	Peritonitis	
164	36–472	7	M	5 mos.	4	2	—	—	22 (3 wks.)	—	452 1025	a, 1.33 g, 3.56	175	310	—	0	0	0	1p	Erysipelas	
165	32–1297	9	F	2 yrs.	0 4	4 0	108/88	15.4 (2 yrs.)	48 (2 yrs.) 99.8 (2 wks.)	—	—	a, 0.6 g, 3.16	180	455	56	0	0	0	1p	Streptococcic peritonitis	
166	30–159	12	F	7 mos.	3	4	110/80	10.3 (7 mos.) 61.2 (1 day)	—	67 (7 mos.) 42 (1 mo.)	—	—	130	460	45	0	0	2	3	Streptococcic peritonitis	Hematuria crescents
167	0–38–820	13	F	5 mos.	2 4	4	116/82	—	—	—	609	2.71 4.2	170	425	—	—	0	0	2	Pneumococcic peritonitis	
168	30–1856	20	F	22 mos.	1 4	2 4	140/70 (22 mos.) 222/134	77 (22 mos.) 102	—	54 (22 mos.)	—	—	484	254	45	0	10	2	3	Uremia, pneumococcic	Followed sore throat

167	0–38–820	13	F	5 mos.	2 4	4	116/82	—	—	—	609	2.71 4.2	170	425	—	—	0	0	2	Pneumococcic peritonitis	
168	30–1856	20	F	22 mos.	1 4	2 4	140/70 (22 mos.) 222/134 (4 mos.)	77 (22 mos.) 102 (1 day)	—	54 (22 mos.)	—	—	484	254	45	0	10	2	3	Uremia, pneumococcic bacteriemia	Followed sore throat
169	30–768	21	M	—	3	4	180/100 (1 wk.)	53.9 (9 days)	—	—	—	—	387	549	—	0	0	2	2	Peritonitis	
170	32–1080	31	M	6 yrs.	1 4	2	158/96 (6 mos.) 236/176	—	41.4 (6 mos.) 166.5	65 (6 mos.) 5	—	a, 0.9 g, 2.6	525	400	69	0	10	3	3	Uremia	Retinitis
171	34–1536	32	F	2 yrs.	4	3 0	130/98 (2 yrs.) 190/112	31.2 (2 yrs.) 120.4	—	50 (2 yrs.) 0	230	a, 1.49 g, 1.09 f, 0.66	440	170	44	0	70	3	3	Uremia	
172	28–183	34	F	7 mos.	3	3 0	200/140 (1 mo.)	47 (1 wk.)	—	0 (1 wk.)	—	—	300	300 (one)	48	—	0	1	2	Broncho-pneumonia	
173	35–654	36	M	5 wks.	4	3	108/74	—	38 (2 wks.)	—	—	a, 1.0 g, 0.9 f, 0.7	280	365	73	—	0	0	1p	Accident	
174	37–2146	36	M	1 yr.	3	3	130/90 (2 mos.) 160/120	28.7 (2 mos.)	—	15	423	a, 2.97 g, 1.83 f, 0.33	340	420	70	—	0	0	1		
175	25–636	37	M	5 yrs.+	2 1	2	150/120 170/120 (2 mos.)	31 (2 mos.) 159 (5 days)	—	—	—	—	450	375	—	1	50	3p	3	Uremia	
176	35–961	40	M	9 mos.	3	4	130/90 (8 mos.) 114/74	18 (8 mos.)	36 (8 mos.)	65 (8 mos.)	258	a, 1.76 g. 1.68 f, 0.46	325	485	—	1	0	0	2	Bacterial endocarditis	Followed sore throat
177	32–1127	43	M	7 yrs.	4	4	Normal to 250/?	Normal to very high	—	—	—	—	500	225	—	0	90	4	3	Uremia	5 yrs. as pure type
178	31–1408	48	M	4 mos.	4	2 4	148/102 (4 mos.) 162/104 (1 mo.)	—	77 (4 mos.) 95 (1 day)	55 (4 mos.)	—	—	Normal	305	—	0	10	2	3	Inanition	
179	17–145	54	M	1 yr.	2	4	155/80 190/95	13 (10 mos.) 23 (10 days)	—	72 (10 mos.)	—	—	320	450	—	—	10	1p	2	Purulent bronchitis	
180	35–114	58	M	3.5 mos.	3	3	140/90	15.9 (2 wks.)	—	44 (2 wks.)	—	a, 1.91 g, 2.62	250	270	56	0	0	0	2	Streptococcic peritonitis	
181	26–827	62	F	15 yrs.	3	3	134/82 (2 days)	25 (1 day)	—	—	—	—	330	260	40	0	0	0	4	Severe anemia	

Under plasma proteins, a = albumin, b = globulin, f = fibrinogen.

there were repeated attacks of peritonitis. The exacerbations often followed an upper respiratory infection. The duration of symptoms was only 5 and 6 weeks in Cases 173 and 157, and these might appropriately be classified as acute, but the duration in the other cases warrants the diagnosis of subacute or chronic.

Cardiac hypertrophy was found in those who died of uremia.

The Structural Alterations in the Kidneys: The convoluted tubules often contain numerous droplets of lipoid, but they never show primary degeneration or necrosis. Atrophy of the tubule occurs only when the capillaries of its associated glomerulus become obstructed; there is no primary tubular atrophy. Lipoid nephrosis is not a primary tubular disease.

In 6 instances there were no visible changes in the capillary basement membranes. Cases of this type have been reported by several writers and have given rise to the widespread belief that in lipoid nephrosis the glomeruli are normal. It appears from our study (Table X) that in young children the basement membranes either show no thickening at all (Fig. 9) or only focal areas of thickening (1p, in Table X), while in older children and adults thickening of the basement membranes is nearly always pronounced. The absence of thickening is not due entirely to a short duration of the disease, since in 3 cases without thickening the duration was 13 mos., 15 mos. and 16 mos. respectively. It seems highly improbable that these cases with normal appearing capillaries represent a different disease from those with thick membranes, since the clinical features of the two groups are almost identical and there are numerous gradations from normal membranes to those that are very thick. In view of the remarkable permeability of the capillaries to the plasma proteins one must believe that the capillary walls, *i.e.* the basement membranes, are injured even though they show no structural changes. The capacity of the membrane to thicken in response to the injury is in some way related to age.

In Cases 164, 165 and 173 there were individual glomerular lobules here and there with thick basement membranes, and in Case 161 there were a few glomeruli with marked diffuse thickening of the basement membranes (Fig. 10). Blackman noted a few hyaline glomeruli in several of his cases, but explained them as a result of focal glomerulonephritis. However, these individual glo-

meruli show the same thickening of the basement membranes as is found in the diffuse form.

Tubular atrophy occurs when the thickened basement membranes have produced marked narrowing or closure of the glomerular capillaries. Complete closure of the capillaries results in hyalinization of the glomerulus and extreme atrophy of its tubule. When a large proportion of the glomeruli have become hyaline the kidneys may shrink in size and uremia develops (Cases 171, 175 and 177) (Fig. 11). It is to be noted that the contracted kidneys of lipoid nephrosis are due to primary glomerular disease with secondary tubular atrophy and not to primary tubular degeneration as Th. Fahr maintained. When a small proportion of the glomeruli are hyaline (Cases 178, 179) a patchy type of atrophy develops. A diffuse tubular atrophy of moderate degree develops when all the glomerular capillaries are narrowed but not completely closed (Cases 166, 168, 169, 170, 171) (Fig. 12). Uremia may develop in this way before any large proportion of the glomeruli have become hyaline (Case 170).

The Relation of Hydropic Glomerulonephritis (Lipoid Nephrosis) to the Azotemic Type

In the foregoing discussion we have presented clinical and anatomical evidence that lipoid nephrosis is a glomerular and not a tubular disease, but since this view is not widely accepted at present a brief historical résumé of the subject may be helpful.

Prior to 1914 lipoid nephrosis was known as parenchymatous nephritis. It was well known that edema and albuminuria were outstanding features, that uremia seldom developed, and that the kidneys were usually large. At that time azotemic glomerulonephritis and the hypertensive kidney were regarded as disease of the interstitial tissue, "interstitial nephritis" in contrast with the "parenchymatous" type which was vaguely considered tubular disease.

The identification of glomerulonephritis by Langhans and Löhlein and of vascular disease by Ziegler initiated the modern period of renal investigation. The popular monograph by Volhard and Fahr in 1914 [7] created widespread interest in nephritis, but their effort to establish "nephrosis" as an entity has retarded progress. These writers classed as nephroses all renal diseases which

they considered degenerative in nature, such as the effects of chemical and bacterial poisons, amyloid disease, eclampsia and genuine or lipoid nephrosis. These diseases have little in common either clinically or pathologically and nothing is to be gained by placing them in one group. In recent years "nephrosis" has been restricted by most writers to lipoid nephrosis.

Volhard and Fahr distinguished two forms of lipoid nephrosis — pure nephrosis and nephrosis with a nephritic component. They believed that nephrosis and nephritis are distinct diseases, the former being degenerative in character, the latter inflammatory. When a patient with the nephrotic syndrome (albuminuria, edema, and so on) developed hypertension or uremia, they believed that nephritis had been superimposed on nephrosis. They stated that pure nephrosis shows only tubular degeneration and that nephritis shows inflammation in the glomeruli. These ideas are still widely supported by clinicians and pathologists.

Another theory of lipoid nephrosis that has many adherents is that it is a general metabolic disorder with secondary renal changes. This view was supported by Epstein [8] who wrote of "albuminuric diabetes." Diebold,[9] Wolbach and Blackfan [10] and others do not believe that the renal lesions are responsible for the symptoms.

It is customary to describe two forms of lipoid nephrosis — the pure type and the mixed type. There are many who believe that these forms are distinct and that the mixed type is a form of glomerulonephritis; others regard the mixed type as a mixture of nephrosis and nephritis, and a few believe that nephrosis is merely a variety of glomerulonephritis.

(*A*) *Pure Lipoid Nephrosis:* This disease is characterized clinically by the presence of marked edema, albuminuria, hypercholesterolemia and low plasma proteins, and by the absence of hypertension, hematuria and renal insufficiency. Pathologically the usual descriptions emphasize the presence of abundant lipoid in the renal tubules and the absence of glomerular disease.

There is disagreement in the literature as to the clinical limitations of the disease. The most rigid definition is given by Leiter [11] who excludes from this group every case in which there is hematuria, any elevation of blood pressure or any renal insufficiency. Volhard [12] apparently holds a somewhat similar view. But the

majority of writers adopt a more elastic definition. Gainsborough [13] found hematuria at the onset of the illness in 6 of 10 cases, and several other writers mention hematuria in an occasional case. One of our cases, Case 168, showed hematuria. Blackman [14] does not exclude cases that show transitory hypertension or increases of non-protein nitrogen, but he would reject any case with a constant or progressive increase of non-protein nitrogen or of blood pressure. He would also reject those with gross hematuria. Many of our cases in Table IX would be admitted by Blackman's definition but would be excluded by Leiter's. When the patient is studied thoroughly with repeated and varied functional tests some degree of nitrogen retention will usually be found at times. The blood urea may be somewhat elevated early in the disease but normal later on (Cases 158 and 162). These variations are probably due to extrarenal influences.

With regard to the pathological changes in the kidneys the great majority of authors find the glomeruli normal. Blackman found a few hyaline glomeruli with atrophic tubules in several of his cases. There were focal thickenings of the basement membranes in 4 of our cases (Cases 161, 164, 165 and 173). In Case 166 there was a marked diffuse thickening of all the basement membranes with a beginning diffuse tubular atrophy, but some would reject this case because of the high urea nitrogen on the day of death.

(*B*) *The Mixed Type of Lipoid Nephrosis:* As noted above, this disease has all the positive features of the pure type but has in addition either azotemia or hypertension, or both conditions. In the literature there are three theories in regard to the nature of this disease: (1) that it is a form of glomerulonephritis entirely distinct from pure lipoid nephrosis; (2) that it is a nephrosis with a superimposed nephritis, or *vice versa*; and (3) that it is a variety of glomerulonephritis closely related to pure lipoid nephrosis and that its special symptomatology is due to the anatomical nature of its glomerular lesions.

Many writers discuss the "nephrotic syndrome" or nephrosis including cases of both the pure and the mixed types, and do not concern themselves with the anatomical nature of the lesion.

(1) The view that pure nephrosis is different from the mixed type is supported by many writers on the basis of their experience. They have observed cases of nephrosis without persistent hyper-

tension or azotemia where the individual either recovered entirely or died of an infection, usually peritonitis. At postmortem no proliferative glomerulitis was found. But these writers offer no explanation for the cases that exhibit the symptoms of pure lipoid nephrosis for some years and then develop hypertension and uremia. Several such cases are now on record. Volhard [12] mentioned a case of nephrosis in a boy 7 years of age, who developed clinical evidence of a nephrotic contracted kidney. Débre and Marie [15] reported the case of a child 5 years of age who died in uremic coma after a period of 3 years of pure lipoid nephrosis. Gainsborough [13] reported that one of his patients had nephrosis for 8 years and developed slight hypertension and nitrogen retention during the last few months of life. A remarkable case was reported by George Fahr [16] (Case 177). The patient, a physician, was 36 years of age at the onset of his illness. For 5 years he had a typical picture of pure lipoid nephrosis and was studied carefully in several prominent clinics. During the last 2 years of his life he gradually developed hypertension and azotemia, and died with a very high blood pressure and a marked elevation of blood urea.

It is, therefore, well established that pure lipoid nephrosis may pass gradually into the mixed type, developing hypertension and uremia. Those who insist on the separate identity of the pure and mixed types can only suppose that nephritis has been superimposed on the nephrosis, but as we shall show presently no new disease has been introduced but the glomerular capillaries have been progressively narrowed and closed by thickening of the basement membranes.

(2) The second view is that the mixed type is a mixture of two diseases, *i.e.* nephrosis and nephritis. This view was first promulgated by Volhard and Fahr who used the expression "nephritis with a nephrotic Einschlag." It is not entirely clear what these authors meant by a "nephrotic Einschlag." Volhard explained some years later that he meant nephritis with a tendency to edema, but Fahr has stated definitely that nephrosis is something quite distinct from nephritis.

The erroneous view has been widely accepted that albuminuria and edema indicate nephrosis and that hypertension and azotemia mean nephritis. But albuminuria and edema occur also in nephritis although usually in lesser intensity, and consistency re-

quires the advocates of this theory to admit some nephrotic component in most cases of nephritis. There is no feature of nephrosis that does not occur also in some cases of nephritis. Furthermore it has been clearly established that albuminuria and edema are due to glomerular and not to tubular disease.

(3) The third theory postulates that the mixed type of lipoid nephrosis is a variety of glomerulonephritis closely related to pure lipoid nephrosis, and that its symptoms may be explained by the nature of the glomerular lesions. We have advocated this interpretation for several years.

Résumé of the Pathology of Hydropic Glomerulonephritis (Lipoid Nephrosis): The clinical syndrome, commonly called lipoid nephrosis, is not associated with a uniform type of glomerular lesion. In 6 of our 40 cases there was a proliferative glomerulonephritis but most of the glomerular capillaries were patent, allowing the escape of serum proteins into the urine and thus favoring the development of edema.

In 6 young children there were no visible changes in the glomeruli. In 3 children and 1 adult individual glomeruli or individual glomerular lobules showed thickening of the capillary basement membranes. In the other 24 cases there was a definite diffuse thickening of the membranes. Two children, aged 12 years and 13 years respectively, showed this membranous change as strikingly as the adults. In nine adults (Table IX) some glomerular lobules showed proliferative changes. In 3 of the 4 cases with death from uremia a large proportion of the glomeruli were hyaline.

Apart from the 6 cases of proliferative glomerulonephritis mentioned above, lipoid nephrosis was associated with a membranous type of glomerulitis when any lesions were visible. There were no clinical distinctions between the 2 cases in children (Cases 166 and 167) with thick membranes and those with normal membranes. In those with diffuse thickening of the basement membranes hypertension was present in 14 and absent in 8 cases.

A moderate tubular atrophy develops when the glomerular capillaries become so narrow that they transmit a decreased amount of blood (Cases 166, 169 and 178), and the tubules disappear almost completely after the glomeruli become hyaline. The glomeruli are obliterated by progressive thickening of the

basement membranes. In the cases with death from uremia tubular atrophy is very pronounced. The atrophy of the tubules is not due to primary tubular disease but is secondary to the closure of the glomeruli. The "nephrotic contracted kidney" results from membranous glomerulonephritis.

Discussion

In the various forms of glomerulonephritis the symptoms and the clinical course are closely dependent upon the character and the extent of the glomerular lesions. If the initial acute attack results in widespread severe capillary obstruction renal insufficiency soon develops. Those cases that terminate in uremia within a few months are called acute, while those that survive from 4 or 5 months to 1 year are usually called subacute. When the initial glomerular injury is less intense so that a majority of the capillaries remain more or less permeable a chronic nephritis develops. Complete anatomical recovery evidently takes place after mild acute glomerulonephritis. The initial lesions are less severe and extensive in the cases that become chronic than in those that follow a subacute course.

The initial glomerular lesion consists of an increase of endothelial cells and splitting and fragmentation of the central capillary basement membranes in the interior of the lobules (Fig. 4). If the capillaries become completely occluded the glomerulus becomes hyaline; if partially occluded a peripheral circulation develops in the lobule and the hyaline fibers, derivatives of the central membranes, become fused into a hyaline mass at the center of the lobule (Figs. 3 and 7). The glomeruli shown in Figures 2, 3 and 7 represent the usual structure of functioning glomeruli in chronic azotemic glomerulonephritis. Their structure is definitely altered but evidently glomerular filtration is not notably reduced since the associated tubules are not atrophic.

In latent chronic glomerulonephritis nearly all of the glomeruli have a structure similar to that shown in Figures 2 and 3. If the lesion does not progress beyond this stage renal function remains adequate. In advanced chronic glomerulonephritis many of the persistent glomeruli have a structure similar to those of the latent stage. The chief difference between the latent and advanced stages is that in the latter most of the glomeruli are either hyaline

or markedly obstructed. Azotemic glomerulonephritis is characterized by obstruction of the glomerular capillaries.

In hydropic glomerulonephritis the capillary walls are injured but the lumens remain open. This type of lesion seldom occurs in proliferative glomerulitis but it is characteristic of membranous glomerulitis. It is not known whether or not membranous glomerulitis has a different etiology from the proliferative form; we know only that in the proliferative type the capillaries become obstructed, while in the membranous form the capillary walls are injured and become permeable to the plasma proteins. The marked permeability of the capillaries to proteins causes edema, which is the outstanding feature of the disease. Hypertension does not develop until the thickened membranes have produced a definite narrowing of the capillalry lumens. Extreme thickening of the membranes may result in extensive hyalinization of the glomeruli and renal insufficiency. For some unknown reason hydropic glomerulonephritis in young children seldom shows extensive thickening of the basement membranes.

Azotemic nephritis is due to capillary obstruction and hydropic nephritis results from increased permeability of the capillaries to proteins. Azotemia develops regularly in proliferative glomerulitis but infrequently in the hydropic form. Hydropic glomerulonephritis is usually due to membranous glomerulitis, occasionally to the proliferative form.

Summary

Of 181 cases of glomerulonephritis, 16 were classified as subacute, 8 as latent chronic, 117 as chronic azotemic and 40 as chronic hydropic.

In subacute glomerulonephritis the kidneys are not contracted. There is widespread severe glomerular obstruction with well advanced uniform tubular atrophy. There are few hyaline glomeruli.

There are 125 cases of chronic azotemic glomerulonephritis. Eight cases of latent chronic glomerulonephritis are described in which death was due to an intercurrent disease. Only 1 such case has been reported previously. There are only a few hyaline glomeruli and there is little or no tubular atrophy. The glomeruli are all damaged to some degree, their lobules showing hyaline central portions and peripheral capillaries.

Thirty cases of chronic azotemic glomerulonephritis are reported in which there is a history of an initial acute attack. The total duration varied from 1.5 years to 26 years, with an average duration of 10 years. In 15 of the 30 cases the acute attack was followed by a latent chronic stage varying from 1 year to 24.5 years in length; in the remaining 15 cases the acute stage passed directly into active chronic nephritis.

In 30 per cent of the cases the systolic blood pressure was 200 mm. Hg. or higher.

There is some degree of chronic passive congestion of the liver in nearly one-half of the cases, indicating some degree of heart failure, but there is no evidence that heart failure is ever more than a contributing cause of death since all of the patients had uremia. Heart failure may occasionally be a contributory cause of edema. Only one patient had a history of apoplexy and only one had an attack of coronary sclerosis.

Retinitis was found in 35 of 46 cases in which the eyegrounds were examined. There is a definite relation between high blood pressure and retinitis.

There is no relation between the weight of the kidneys and the duration of the disease or the height of the recorded blood pressure. The kidneys are occasionally of normal size or even enlarged in the terminal stages. Large kidneys contain a high proportion of injured glomeruli with moderately atrophic tubules, while small kidneys consist largely of hyaline glomeruli with extremely atrophic tubules.

Forty cases of hydropic glomerulonephritis (lipoid nephrosis) are reported. In 6 of these the glomerular structure was that of chronic proliferative glomerulonephritis, and in 9 others there was a mixture of proliferative and membranous glomerular lesions with the latter in great preponderance. In the remaining 25 cases there were no proliferative lesions.

In 6 cases in young children there were no visible changes in the glomerular capillaries, and in 3 other children there were only focal membranous lesions.

With one exception diffuse thickening of the basement membranes was present in all persons over 12 years of age.

In 4 cases membranous glomerulitis produced such an extensive narrowing of the glomerular capillaries that uremia developed.

When a patient with pure lipoid nephrosis develops hypertension and uremia no new disease is superimposed — there is merely progressive thickening of the basement membranes.

Nephrosis is a form of glomerulonephritis in which the glomerular capillaries remain open and allow the blood proteins to escape into the urine. In proliferative glomerulonephritis the capillary lesions are nearly always of obstructive type.

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DESCRIPTION OF PLATES

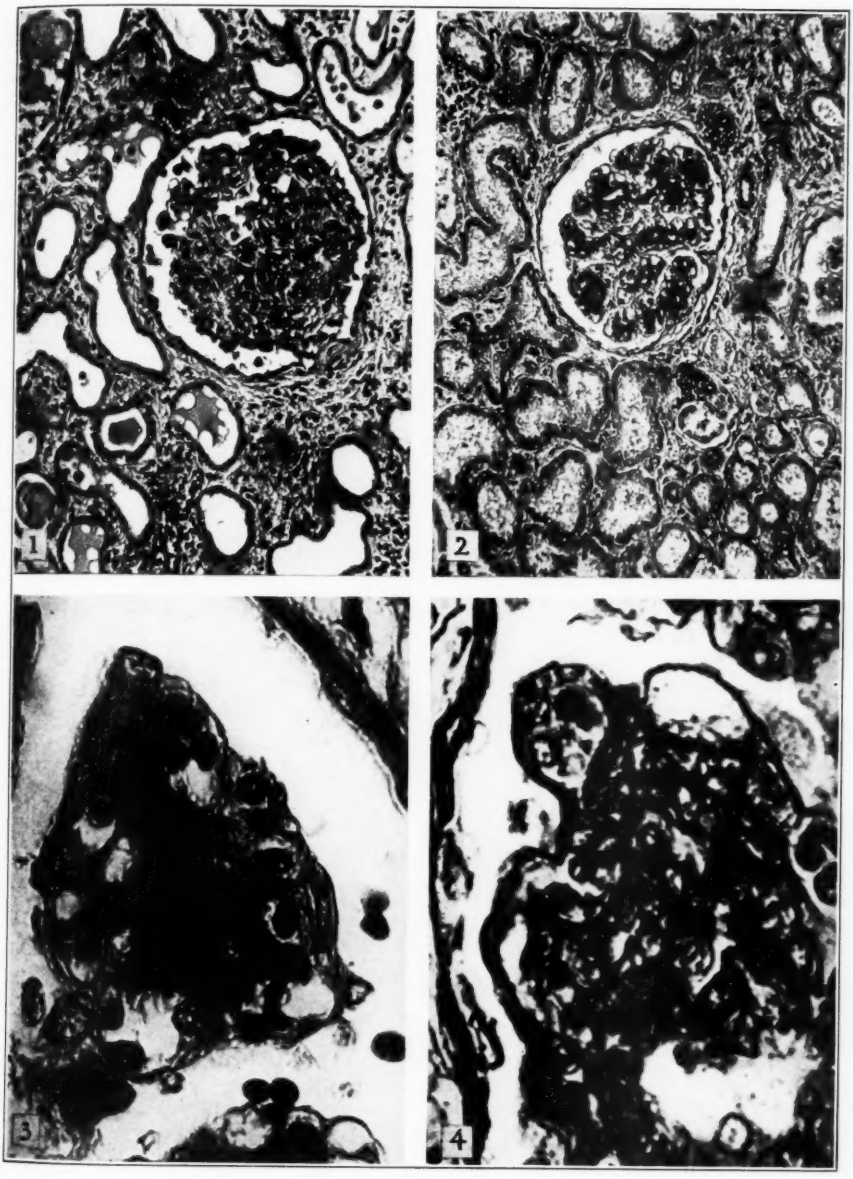
PLATE 142

FIG. 1. Case 2. Subacute glomerulonephritis. Note obstruction of glomerular capillaries and moderate tubular atrophy. × 200.

FIG. 2. Case 18. Latent chronic nephritis. Note absence of tubular atrophy. The glomerular lobules show solid central portions with peripheral capillaries. × 200.

FIG. 3. Case 18. Latent chronic nephritis. Detailed structure of glomerular lobule. Note hyaline central portions of lobule and peripheral capillaries. × 850.

FIG. 4. Glomerular lobule from mild acute glomerulonephritis. Note fragmentation of the central capillary basement membranes and partial permeability of capillaries. This is probably the type of lesion that becomes chronic. × 850.



Bell

Subacute and Chronic Glomerulonephritis

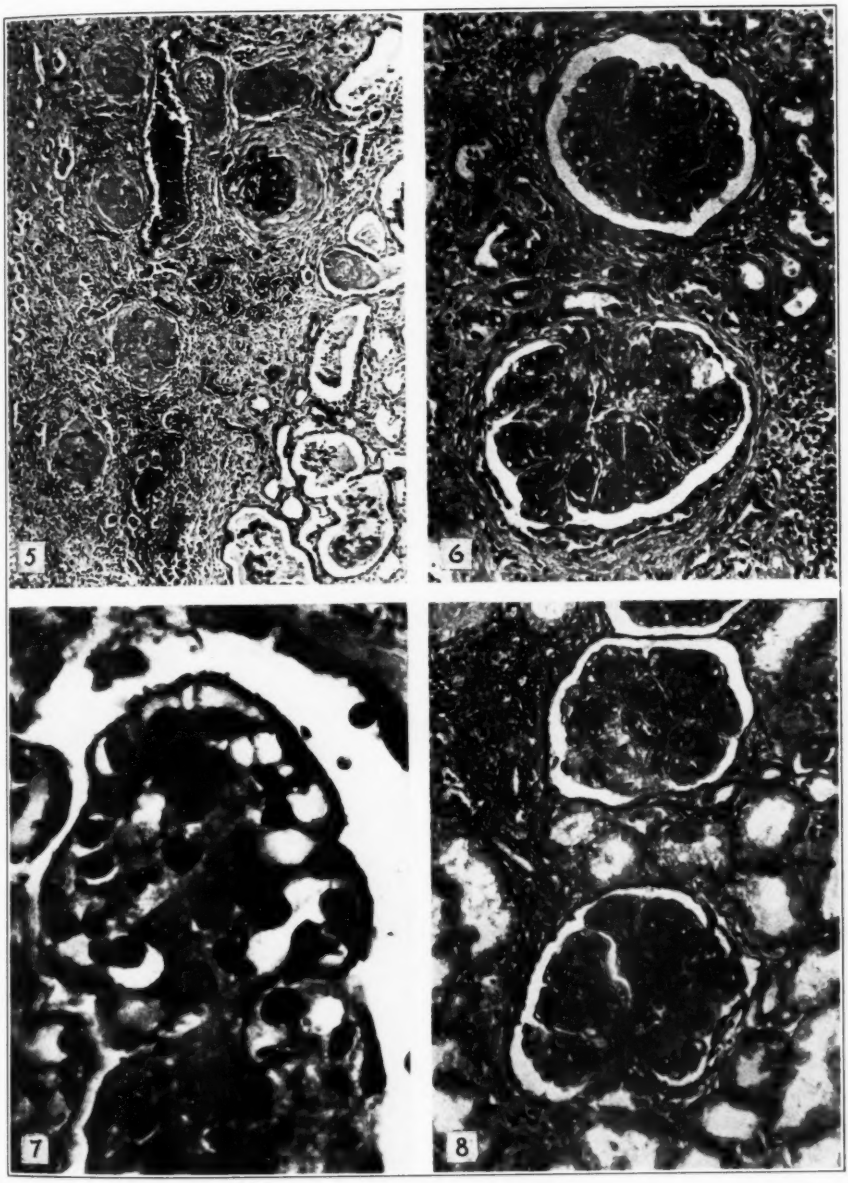
Plate 143

Fig. 5. Case 93. Chronic azotemic glomerulonephritis with contracted kidneys. Histological type *a*. Note large proportion of hyaline glomeruli. × 80.

Fig. 6. Case 25. Chronic azotemic glomerulonephritis with uremia. Weight of kidneys 460 gm. Duration 4 years. Histological type b_1. Partially obstructed glomeruli with well advanced tubular atrophy. × 200.

Fig. 7. Case 57. Chronic azotemic glomerulonephritis with uremia. Histological type b_1. Lobule of a glomerulus showing central hyaline mass and peripheral capillaries. × 850.

Fig. 8. Case 142. Group IV. A. Chronic hydropic glomerulonephritis with the microscopic structure of proliferative glomerulonephritis. × 200.



Bell Subacute and Chronic Glomerulonephritis

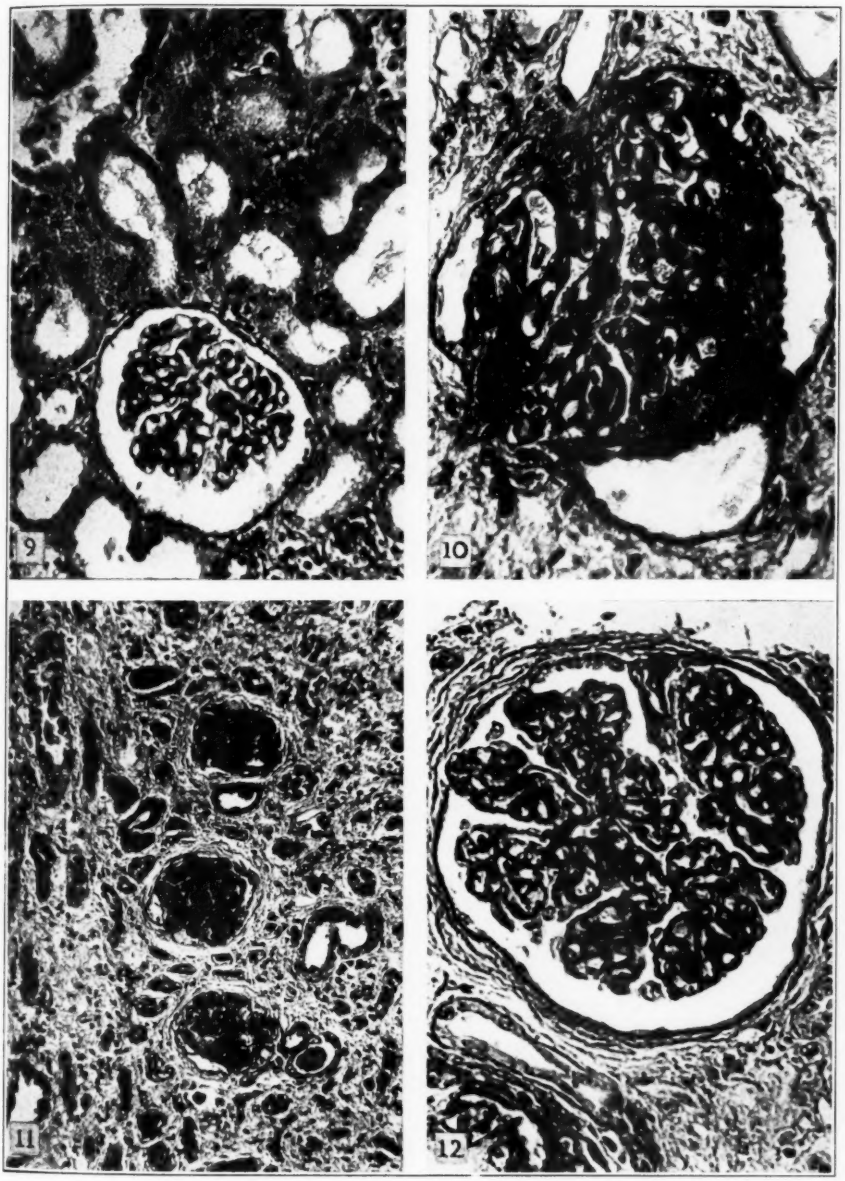
PLATE 144

FIG. 9. Case 164. Hydropic glomerulonephritis in a child 7 years of age. There are no structural changes in the glomeruli. × 200.

FIG. 10. Case 161. Hydropic glomerulonephritis in a child 5 years of age. A majority of the glomeruli show no changes. The illustration shows an individual glomerulus with diffuse thickening of the basement membranes. Mallory-Heidenhain stain. × 400.

FIG. 11. Case 171. Chronic hydropic glomerulonephritis with contracted kidneys and uremia. Note small hyaline glomeruli and atrophic tubules. × 150.

FIG. 12. Case 168. Chronic hydropic glomerulonephritis. A glomerulus stained by the Mallory-Heidenhain method. Ninety per cent of the glomeruli were of this structure. Note the thick basement membranes. × 400.



Bell

Subacute and Chronic Glomerulonephritis

ACUTE HEMATOGENOUS INTERSTITIAL NEPHRITIS *

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INTRODUCTION

In acute hematogenous interstitial nephritis the kidney is usually enlarged and soft, the parenchyma moist, and the glistening cut surface reveals a grayish streaking of the thickened cortex. Histological examination shows that the tubules are separated by interstitial accumulations of fluid with varying amounts of cellular exudate. Most pathologists are familiar with this condition but little attention hitherto has been paid to it. The lesion is encountered most frequently incidentally at autopsy and, since no disturbance of renal function is generally suspected, the findings are considered to be irrelevant. Occasionally, however, cases are observed where failure of renal function, progressive oliguria and uremia are outstanding features and interstitial nephritis is found to be the only, or at least the most prominent, morphological finding. This has prompted Fahr and others to recognize interstitial nephritis as a disease entity. Fahr states that this type of "inflammatory swelling of the kidney is of importance because it may result in oliguria and possibly anuria with subsequent uremia."

Although it is true that interstitial nephritis may occasionally gain considerable significance, we know as yet little about its pathogenesis, its correlation to functional disturbances and simultaneous changes in any other organs. Interstitial nephritis is not much more than a mere morphological concept. Our knowledge of the multitude of conditions anteceding or causing this lesion in the kidney is incomplete. The denominator common to all has not yet been found. We are still unable to decide to what extent the renal lesion participates in the production of coinciding anuric uremia. Although extrarenal factors seem to play a dominating rôle, it has been shown that the kidney function is actually disturbed.

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The following study was prompted by the observation of several very striking cases of interstitial nephritis with anuria and uremia. These and a number of "silent" cases of interstitial nephritis, found incidentally at autopsy, will be reported briefly, and their significance in regard to the above mentioned problems will be discussed.

Case Reports

Case 1. Mrs. M. A. (A–2306), a pregnant white female, 33 years of age, was admitted to the Memorial Hospital with the chief complaint of discharge from the vagina and persistent vomiting. Five days previously the patient had inserted a rubber catheter into the cervix. The pregnancy had progressed

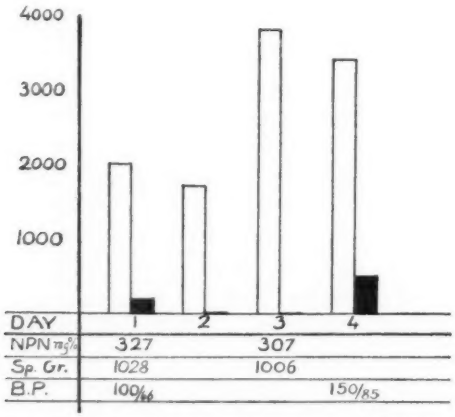

Chart 1. Case 1, A–2306. White column = fluid intake. Black column = urine output.

uneventfully, but 2 days before admission to the hospital she began to have abdominal cramps, following which a large blood clot was passed. Since then she had had a continuous, foul smelling, blood-tinged vaginal discharge. She had one chill and the night before admission began vomiting everything, including fluids. There had been no bleeding for the past 8 days. The past history was insignificant.

Physical Examination: A soft systolic murmur was heard at the apex of the heart. The blood pressure was 100/56 mm. Hg. The uterus was not palpable and there was no tenderness or rigidity. There was a foul smelling, grayish white vaginal discharge but no bleeding. The physical examination was otherwise negative.

Course of Illness: The patient continued to vomit, the vomitus containing small amounts of bright red blood. The abdomen became slightly distended and tender. The temperature ranged between 98° and 100° F., and death occurred in uremia.

Autopsy Diagnoses: Infected postabortive endometrium; acute gangrenous appendicitis; fibrinous pericarditis; pulmonary edema and atelectasis; bilateral hydrothorax; ascites; and old, healed endocarditis of mitral valve.

Kidneys: Weight 250 gm. each. In gross the characteristic picture of interstitial nephritis, except for the presence of punctate hemorrhages on the surface, was seen. The differential diagnosis between acute early glomerulonephritis and interstitial nephritis could not be made in gross.

Histological Examination: There is severe edema with separation of the tubules. The cellular infiltration, which is slightly more marked in the medulla than in the cortex, consists mainly of small round cells and polymorphonuclear leukocytes. The pelves are free from infiltration. The tubules are markedly dilated. Degenerative changes of epithelial cells is negligible. Hemoglobin and hematin casts are present. The glomeruli show questionable intercapillary edema but no inflammation.

Summary: The case is that of an abortion with infected placental residue and acute gangrenous appendicitis. There was no septicemia. Severe oliguria and temporary anuria developed, for which circulatory failure cannot be considered the cause (terminal blood pressure 150/85 mm. Hg.). The specific gravity of the urine was low toward the end, the blood pressure raised, the nonprotein nitrogen high, and death occurred in uremia with uremic pericarditis.

The interstitial nephritis in this case is of the serous type.

Case 2. W. S. P. (A–2156), a white female, 33 years of age, was admitted to the Memorial Hospital because of jaundice, abdominal pain, chills and fever. After missing a menstrual period the patient considered herself pregnant and took one drachm of ergot 3 times daily for 2 weeks. Two days before admission she took a lysol douche. A short time following this she began to have vague generalized abdominal pains which became more severe, and abdominal tenderness became marked. Jaundice developed 1 day before admission and was increased in intensity. She had fever, chills, headache, pain and edema of the ankles, bleeding from the vagina, and syncope with unconsciousness occurred the night before admission.

Physical Examination: The patient was a well developed and well nourished white obese female, markedly jaundiced. The temperature was 103.8° F., the pulse 114, the respiration 24, and the blood pressure 70/10 mm. Hg. The heart sounds were faint and distant. There were no signs of pulmonary disease. The abdomen showed no tenderness. A slight edema of the lower extremities was present.

Course of Illness: The treatment consisted essentially of supportive measures. Parenteral fluids and transfusions of blood (approximately 400 cc.) were given on the 1st, 2nd, 3rd, 4th, 7th, 8th, 11th, 12th and 13th days. The temperature ranged between 99° and 103° F. The patient's condition became progressively worse and twitching of the muscles of the face developed 2 days ante mortem with convulsions the night before death. She died in uremia 16 days after admission.

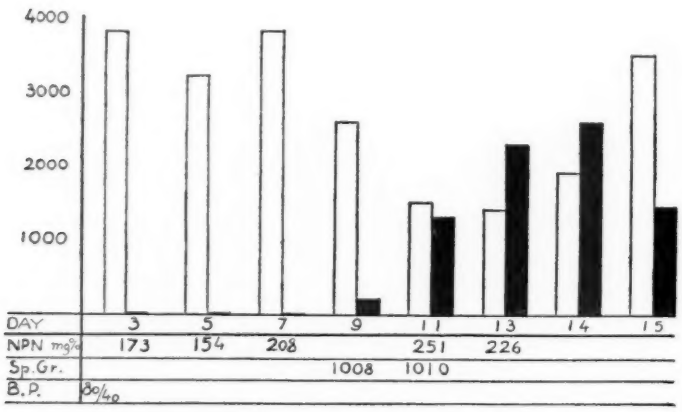

Chart 2. Case 2, A–2156. White column = fluid intake. Black column = urine output.

Autopsy Diagnoses: Severe chemical burns of the vagina with excoriation of the skin and external genitalia; marked edema of the urinary bladder; and confluent bronchopneumonia of the right upper lobe.

Kidneys: Weight 350 gm. each. The grossly typical picture of interstitial nephritis was seen.

Histological Examination: There is severe intertubular edema. The cellular infiltration is evenly distributed between the medulla and the cortex and consists of small round cells, plasma cells, eosinophils and a few polymorphonuclear leukocytes. The tubules show severe dilatation with marked degenerative changes including occasional epithelial necrosis. Hemoglobin and hematin casts are present in almost all collecting tubules of the medulla. Most of the tubules are seemingly blocked by hematin casts. The glomeruli are essentially negative.

Liver: There is moderate degeneration of the liver cells, char-

acterized by basophilic granulation and a great irregularity of the nuclei with dissociation of liver cells in the center of the lobules.

Summary: The case is that of a chemical burn of the vagina and skin of the external genitalia followed by severe toxemia and jaundice. There was no septicemia. The condition was associated with temporarily complete anuria, the specific gravity of the urine was low, the non-protein nitrogen was raised, and death occurred in uremia in spite of reestablished urinary excretion.

The interstitial nephritis at the time of death was most severe and of the serous type.

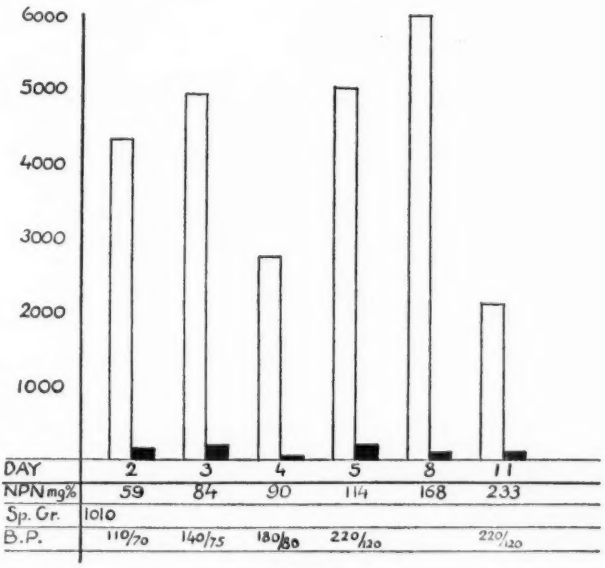

Chart 3. Case 3, A–2003. White column = fluid intake. Black column = urine output.

Case 3. This patient (A–2003), a 43 year old white male, was admitted to the Memorial Hospital on Aug. 25, 1936, complaining of pain over the left kidney of 3 weeks duration. There was a history of some burning upon urination and nocturia. The diagnosis at that time was ureteral calculus with acute pyelitis and pyelonephritis. On Sept. 2, 1936, the patient was operated upon and a ureteral calculus was removed from the left ureter. The blood pressure was 160/110 mm. Hg., the non-protein nitrogen 57, and the urea 38 mg. per cent. Three weeks later the patient was readmitted to the hospital and an intracapsular nephrectomy (left side) was performed Oct. 4, 1936.

The patient was readmitted again on Jan. 1, 1937, complaining of abdominal pain on the right side. There was no cardiac hypertrophy. The blood pressure was 130/90 mm. Hg. Two days after admission he was believed to have an obstruction of the right ureter and a right nephrotomy was done. The operative wound continued to drain for 10 days and the patient finally succumbed in uremia. Two blood transfusions were given (500 cc. each) on the 2nd and 7th days.

Autopsy Diagnoses: Absence of left kidney, postoperative; nephrotomy, right; lobular pneumonia in right upper lobe with hemorrhage and abscess formation; fibrinous pericarditis; slight hydrothorax and ascites; and old healed endocarditis of aortic cusps.

Kidneys: The weight was not noted. The organ was greatly enlarged, very moist and in gross typical of interstitial nephritis.

Histological Examination: There is severe edema; the cellular infiltration, much more marked in the cortex than in the medulla, consists of monocytes, lymphocytes, eosinophils and a few polymorphonuclear leukocytes. The pelvis does not show any inflammatory infiltration. The tubules are markedly dilated and show a diffuse and most severe vacuolic disorder of the cytoplasm. There is also rather marked degeneration, occasionally of the necrotizing type. Hemoglobin casts are absent.

Liver: There is extensive vacuolization of the liver cells of the central portion of the lobules, resembling marked glycogen storage.

Summary: The case is that of an interstitial nephritis following pyelonephritis with nephrectomy of the opposite kidney. Absence of pelvic inflammation and the predominance of cortical infiltration indicate that the interstitial nephritis is of hematogenous origin rather than ascending. There was complete urinary suppression with a steadily rising non-protein nitrogen. Circulatory failure can be excluded as the cause of oliguria since the blood pressure rose toward the end to 220/120 mm. Hg.

The interstitial nephritis is of a mixed serous and cellular type.

Case 4. E. C. (A–2073), a negro, 45 years of age, was admitted to the St. Philip Hospital because of severe and extensive burns over the left lower extremities and left hand. A spray of 4 per cent solution of tannic acid was applied with adequate sedation for relief of pain.

Course of Illness: The temperature rose to 103° F. the day after admission, stayed high and rose terminally to 106° F. The patient developed a small abscess at the left elbow 3 days before death.

Autopsy Diagnoses: Extensive burns of the left leg and hand; phlegmon of left elbow; and bronchopneumonia of both lower and upper lobes.

Kidneys: Weight 300 gm. each. The gross appearance was characteristic of interstitial nephritis.

Histological Examination: There is severe edema and cellular infiltration, more marked in the cortex than in the medulla, consisting of many polymorphonuclear leukocytes, eosinophils, plasma

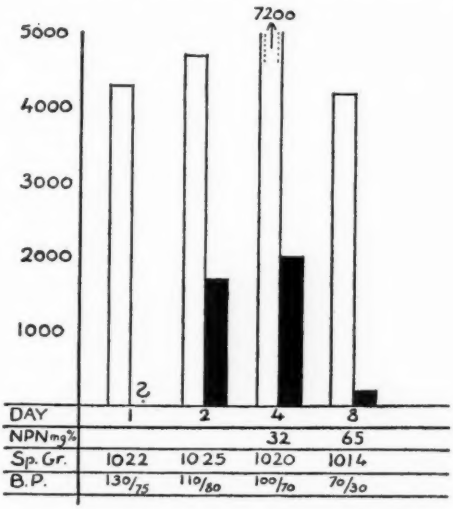

Chart 4. Case 4, A–2073. White column = fluid intake. Black column = urine output.

cells and monocytes. Tubular dilatation is only moderate in degree. Some albuminous deposit is present but there is no evidence of epithelial degeneration. Glomeruli show questionable intercapillary edema.

Liver: There are focal midzonal necroses of liver cells with an accumulation of polymorphonuclear leukocytes. There is a distinct increase of interstitial infiltration consisting chiefly of polymorphonuclear leukocytes.

Heart: The myocardium shows minute foci of interstitial infiltration consisting of monocytes, polymorphonuclear leukocytes and eosinophils.

Summary: The case is one of severe burns with a high toxic temperature, and in spite of forced intake of fluids (7200 cc. in 1 day), the oliguria increased to almost complete anuria. Although circulatory failure may have contributed to urinary suppression, the specific gravity of the urine fell toward the end and the nonprotein nitrogen rose.

The interstitial nephritis, in this case most severe, is of the serous type.

CASE 5. M. R. (A–1989), a negress, 29 years of age, was admitted to the St. Philip Hospital with the chief complaint of severe pain in the right chest. Four days previous to admission she had an attack of pain in the chest, back and neck accompanied by two severe chills with fever, cough and expectoration of blood-tinged sputum. The past history was insignificant.

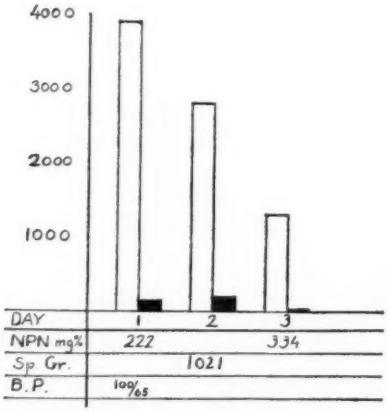

Chart 5. Case 5, A–1989. White column = fluid intake. Black column = urine output.

Physical Examination: This showed a well developed but poorly nourished female. The symptoms indicated lobar pneumonia involving the right middle and lower lobes.

Course of Illness: The patient became progressively worse and severe jaundice was noted on the 2nd day. Dehydration was apparent and the temperature became subnormal. Death occurred on the 4th day.

Autopsy Diagnoses: Atypical lobar pneumonia, right middle lobe and lower portion of right upper lobe, with abscess formation; hemorrhagic bronchopneumonia, right lower lobe; marked jaundice; and hemorrhagic diathesis.

Kidneys: Weight 240 gm. each. In gross they were characteristic of interstitial nephritis.

Histological Examination: The edema is moderate. There is marked cellular infiltration consisting mainly of large monocytes, lymphocytes, eosinophils and a few polymorphonuclear leukocytes. The infiltration is situated mainly in the cortex. Tubular dilatation is slight and degenerative changes are confined to occasional hyaline droplet degeneration.

Liver: The liver shows slight interstitial infiltration with polymorphonuclear leukocytes.

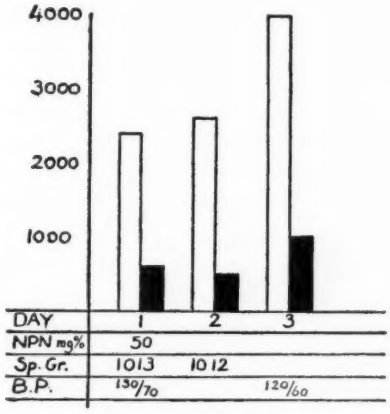

Chart 6. Case 6, A–2013. White column = fluid intake. Black column = urine output.

Summary: The case is that of an atypical pneumonia with abscess formation and severe jaundice which developed 2 days before death. There was almost complete anuria and a rise in nonprotein nitrogen, although circulatory impairment may have contributed to the urinary suppression. It is significant that the urine had a low specific gravity.

The interstitial nephritis is of a more cellular type.

CASE 6. E. W. (A–2013), a negress, 29 years of age, was admitted to the St. Philip Hospital with severe tonsillitis accompanied by general malaise. The onset of illness was 5 days previous. On the night before admission the patient developed pain in the right lower chest and the right upper quadrant of the abdomen. Anorexia was present. Jaundice, associated with itching, developed on the day before admission.

Physical Examination: This showed a well developed but undernourished negress who was markedly jaundiced. The tongue was dry and coated with a raw red border. The tonsils were greatly enlarged and cryptic and the left side of the neck was swollen and tender. The blood pressure was 128/72 mm. Hg. Otherwise the physical examination was negative.

Course of Illness: The patient became progressively worse. The clinical course was characterized by chills, septic temperature and incontinence of urine. Death occurred on the 4th day.

Autopsy Diagnoses: Phlegmon in the soft tissues below the left tonsil and left anterior portion of the neck; thrombophlebitis of jugular vein; multiple pulmonary abscesses; and severe jaundice.

Kidneys: Weight 200 gm. each. In gross they were not remarkable except for a thickened cortex and obscured architecture.

Histological Examination: Marked edema with the infiltrating cells distributed in scattered foci mainly at the medullary cortical junction and consisting of large monocytes, lymphocytes and eosinophils is present. There are a few polymorphonuclear leukocytes. Tubular dilatation is marked, with considerable degeneration of epithelial cells. There are many bile and hemoglobin casts. The glomerular spaces are somewhat dilated.

Summary: The case is that of a septicemia following tonsillitis with thrombophlebitis of the jugular vein and marked jaundice. There was definite oliguria which did not seem to be due to circulatory failure (blood pressure 120/60 mm. Hg.). The specific gravity of the urine was low.

The interstitial nephritis is of the serous type.

Twelve additional cases of interstitial nephritis have also been found during routine autopsies; some of these showed reduced urinary output terminally. The urine, however, was concentrated. In the other cases the clinical observations were not adequate, the patients being moribund when admitted to the hospital. Including all cases, interstitial nephritis was observed under the following conditions:

Five times associated with empyema of the pleural cavity. Isosthenuric oliguria occurred in 1 case in which the non-protein nitrogen, however, did not exceed 50 mg. per cent.

Three times following severe burns (chemical and heat). Isosthenuric oliguria occurred in 2 cases (Cases 2 and 4 reported above).

Three times in the course of septicemia. Isosthenuric oliguria was observed in 1 case (Case 6 reported above).

Twice associated with fever of undetermined origin and jaundice. The cases resembled Weil's disease very closely from both the clinical and the pathological aspects. Spirochetes, however, could not be demonstrated. Oliguria was present in 1 case but was not isosthenuric in character.

Twice in the course of typhoid fever. Oliguria was not observed.

Once following infected abortion and acute appendicitis without septicemia. Hyposthenuric oliguria occurred (Case 1 reported above).

Once following atypical lobar pneumonia. Hyposthenuric oliguria was observed (Case 5 reported above).

Once following nephrectomy of the opposite kidney with oliguria (Case 3 reported above).

In 8 cases the patients were given blood transfusions. Hemoglobin and hematin casts were observed in 5 of these. Two such cases revealed severe histological changes in the kidneys similar to those described in cases of anuria following blood transfusion.

Jaundice was present in 7 cases. The morphological changes in the liver were inconsistent.

Morphology

Gross Appearance of Kidney: Interstitial nephritis may be suspected if the kidney is markedly swollen and if the cut surface reveals an obscured architecture of the cortex which is ill defined from the medulla. The surface is mottled and the color varies from brownish red to gray. A grayish streaking of the cortex on the cut surface is often noticeable. The latter is glistening in contrast with the cut surface of the "nephrotic" kidney, which is dull. Grossly interstitial nephritis may closely resemble the picture of early, acute diffuse glomerulonephritis. In fact, it may be indistinguishable from it since punctate hemorrhages on the surface of the kidney and hematuria may occur in pure interstitial nephritis. In many cases, however, no change in the gross appearance indicates its presence.

Microscopic Examination: Several points deserve critical discussion.

(A) *Nature of the Exudate:* This may vary considerably. In

some cases serous effusion into the lymph spaces with scanty, scattered round cells separates the tubules widely. In other instances the cellular exudate predominates. "Serous" interstitial, or "inflammatory edema," as well as the more cellular type appear to be variations of the same condition. Although the serous type is only found in the early acute phase, the interstitial infiltration, even in the beginning, may be predominatingly cellular in character. There is no definite relationship recognizable between the amount of intertubular effusion and the functional disturbances. Although in the majority of cases rapidly terminating in anuric uremia marked swelling and edema of the kidney are present, exceptions occur.

The cellular exudate is composed of polymorphonuclear leukocytes, eosinophils, lymphocytes, monocytes and plasma cells in various proportions. As Lindau [22] remarks, these infiltrations sometimes resemble hematopoietic foci containing large cells similar to premature myelogenous cells. I have often found this analogy to be striking. Huebschmann's [17] statement that polymorphonuclear leukocytes predominate in very early phases has not been accepted by other investigators (Koch [19] and Fahr [8]). It is likewise my experience that the nature of the cells present varies with the individual cases independent of the stage of the process. It is a remarkable fact that in the acute phase of inflammation small round cells often by far outnumber the polymorphonuclear leukocytes.

(B) *Distribution of Exudate:* Much emphasis has been placed on the distinction between focal and diffuse interstitial nephritis. The focal distribution has been taken as proof of its bacterial origin. Koch [19] deduces that a toxin would act on the kidney diffusely rather than focally. Fahr [8] stresses the difference between the two forms because the diffuse exudative type, in contradistinction to the focal, may result in severe functional disturbances and anuria.

In my observation the cellular exudate in both forms is invariably more or less focal in distribution. It is the serous effusion that diffusely penetrates all lymph spaces. The more cellular the type of inflammation, the more "focal" it appears in distribution. The terms focal and diffuse interstitial nephritis in reality indicate the "cellular" and "serous" type of inflammation between which

there is no essential difference. A distinction, therefore, is not justified.

(C) *Differentiation between Hematogenous and Ascending Interstitial Nephritis:* Most of the cellular infiltrations are found at the corticomedullary junction. This is particularly evident in early interstitial nephritis. The cells are crowded in perivascular lymph spaces. As a rule the cortex reveals a much more extensive cellular exudate than the medulla, which may be entirely free from inflammation. In such cases there is no difficulty in distinguishing this type of "hematogenous" interstitial nephritis from the lymphogenic ascending form. The differential diagnosis, however, may occasionally become exceedingly difficult if the process is diffusely distributed throughout the cortex and medulla and involves the peripelvic tissue. Pyelonephritis does not always ascend within the tubules; it may spread within the lymph channels (see Putschar [27] for literature). Cases have been observed in which severe interstitial nephritis with anuria developed some time after the other kidney had been removed because of calculi and ascending pyelonephritis (Fahr,[8] and Case 3 reported above). In order to establish the hematogenous origin in such instances ureteritis and pyelitis must be ruled out by special examination.

(D) *Involvement of Glomeruli:* Interstitial nephritis may occur in association with diffuse glomerulonephritis. With this exception the glomeruli appear normal, although they may be engorged. The glomerular space is often distended with fluid containing some coagulated plasma and occasionally minute hemorrhages are observed. It must be emphasized, however, that this distention does not involve all the glomeruli and it may be entirely absent in complete anuria where a great number of casts are found in the tubules. Garloch and Klein [10] have described a serous intercapillary glomerulitis in 1 case of interstitial nephritis. In my experience slight swelling and edema of intercapillary connective tissue framework of the glomeruli may be observed occasionally. The lesions in these cases, however, were not noteworthy, with the exception of 1 case in which the intercapillary edema was even accompanied by an accumulation of polymorphonuclear leukocytes between the capillary loops. The intertubular capillaries are invariably markedly engorged and minute hemorrhages are frequently encountered.

(E) *Involvement of Tubular Apparatus:* Tubular changes occur almost invariably. In most instances there is a diffuse though moderate degree of dilatation of the lumens. This is particularly marked in cases of the acute "serous" type of inflammation. The tubules contain coagulated, slightly pinkish staining material. In the more cellular and less edematous cases dilatation may be absent. Degeneration of epithelial cells, as a rule, is slight and appears to be within the range of reversible vacuolic, albuminous or hyaline droplet degeneration of the cytoplasm. Under certain conditions, however, the regressive metamorphosis may be so severe as to resemble the tubular necrosis seen in mercury poisoning. Such changes are obviously irreversible, as evidenced by calcification and epithelial regeneration. Cases of this type have been described by Kuczynski [20] and recently by Goldring and Graef.[11] Their descriptions indicate the presence of interstitial nephritis in addition to the tubular degeneration.

As a rule, the renal tubules remain intact. Occasionally, however, the interstitial infiltration may break through the basement membrane, destroying the epithelial cells and entering the lumen. Polymorphonuclear leukocyte casts are therefore not infrequently encountered.

Other accessory findings, such as bile pigment in epithelial cells, bile casts, hemoglobin and hematin casts, depend on the concomitant or precursory condition causing interstitial nephritis. A parallelism between tubular dilatation, epithelial degeneration and functional disturbance cannot be established.

Conditions Causing Interstitial Nephritis

Infectious Diseases and Septicemia: Interstitial nephritis is known to accompany almost every infectious or septic condition. So frequently is it observed in scarlet fever and Weil's disease that it is regarded as a characteristic complication. Measles, diphtheria, typhoid fever, variola and pneumonic infections are listed among the precursory conditions. It is found also occasionally in tuberculosis, and Fahr [8] assumes that in such instances superimposed streptococcic infections should be taken into account.

The question has often been discussed as to whether the bacteria themselves or their toxins should be held responsible for

these renal changes. It is true that microorganisms sometimes can be found in the kidney, but their demonstration is of little significance. They may circulate throughout the body in instances of septicemia or bacteriemia without causing local reaction. Moreover, a search for bacteria in the kidney in cases of interstitial nephritis has often been in vain (Munk,[24] Kuczynski,[20] and others).

Whether bacteria or their toxins are looked upon as injuring agents, the allergic reaction to various antigens is accepted as the most important factor. Interstitial nephritis is regarded as the reaction of the hypersensitive kidney to either bacteria (Koch [19]) or their toxins (Fahr,[8] and Huebschmann [17]). It should indeed be emphasized that it is the tissue reaction that determines this renal lesion rather than any one specific agent. Interstitial nephritis may even occur without bacterial infection.

Conditions Associated with Hemolysis: Various conditions associated with hemolysis may result in interstitial nephritis. This has frequently been described in anuric uremia following blood transfusion with "compatible" blood. Although most authors have paid much more attention to the formation of hematin casts and tubular degenerative changes, interstitial edema and inflammatory infiltration have frequently been emphasized. The serous type of interstitial nephritis is described in Witts's [32] report of such a case. Lindau [22] stresses more the cellular infiltration. Bordley,[4] reviewing the literature on this subject, finds interstitial cellular infiltration mentioned in 6 out of 9 autopsied cases. Goldring and Graef [11] gave convincing evidence of edematous interstitial nephritis in their cases of death following blood transfusion. Baker [3] lists a varying amount of edema and possibly "chronic inflammatory infiltration" of interstitial tissue among the findings in the kidney in urinary suppression following blood transfusion. He considers these changes to be a late result because they were absent in 1 of his cases which came to autopsy 4 days after transfusion. From a review of the literature, however, it remains uncertain whether or not interstitial nephritis accompanies all instances of anuria after blood transfusion.

One would expect to find similar conditions in black water fever. Autopsy reports, however, do not list interstitial nephritis among the morphological findings. The one histological section of such a

case I had an opportunity to study revealed considerable interstitial infiltration with round cells and some edema.* This lesion may have been neglected in view of the more impressive changes in connection with the hemoglobinuria.

Hepatorenal Syndrome: Interstitial nephritis may, furthermore, occur in what is called the hepatorenal syndrome. It is not my intention to analyze this still somewhat cloudy clinical concept, which comprises a variety of essentially different conditions. I refer at present merely to cases in which impairment of renal function, or better oliguria, anuria and rise of non-protein nitrogen in the plasma follow an acute liver injury. For our purpose it is necessary to distinguish between two types of cases — those in which the preceding liver lesion is of an infectious nature, and those in which the liver injury is non-infectious.

If interstitial nephritis is found to be associated with cholangitis and cholangiolitis, or an interstitial hepatitis, bacteria or their toxins may ultimately be held responsible for the renal lesions as in any other infectious disease.

However, cases are recorded in which "renal involvement" resulted from non-infected liver injuries. Helwig and Orr [13] and Helwig and Schutz [14] reported cases of traumatic liver necrosis in which death occurred in anuric uremia. As a "striking feature" they describe medullary foci of interstitial infiltration with mononuclear cells, eosinophils and plasma cells. Lichtman and Sohval [21] noted acute inflammation of the stroma in addition to tubular degeneration in a case of anuric uremia following subacute yellow atrophy of the liver. The authors interpreted the interstitial infiltration as a reaction to tubular degeneration. This, however, is not tenable in view of the fact that the much more severe tubular degeneration in mercury poisoning is not associated with interstitial infiltration except where there is calcification of epithelial débris, in which case occasional polymorphonuclear cells are found in their immediate vicinity (Fahr [8]). Furthermore, it should be considered that a medullary interstitial infiltration is not likely to result from tubular degeneration in the cortex especially since this region is free from local inflammatory reaction. Thus, irrespective of the interpretation of its pathogenesis we may state that inter-

* I am indebted to Captain DeCoursey, Army Medical Museum, for kindly supplying me with this section.

stitial nephritis is found in hepatorenal syndrome uncomplicated by bacterial infection.

Finally, we have found serous interstitial nephritis mentioned in cases of merely toxic, non-bacterial food poisoning. Nonnenbruch [25] describes such an observation and refers to a similar report by Eppinger.

Correlation of Functional Disturbances with Interstitial Nephritis

Interstitial nephritis may be associated with oliguria, anuria, rise in non-protein nitrogen, and lack of renal concentration power. On the face of it, the urinary suppression appears to be renal in origin. This question is still under discussion and various theories have been advanced to explain the anuria.

Renal Edema and Anuria: Edema and increased intracapsular pressure, in particular on the tubular apparatus, have been held responsible for urinary suppression. This explanation deserves serious consideration in view of the fact that urinary secretion may be restored immediately after decapsulation. However, Koch, who examined a biopsy of a kidney, and also autopsy material from a case of postscarlatinal interstitial nephritis associated with anuria, came to the conclusion that the edema does not cause the anuria. He found that the tubules are of normal caliber and that the glomerular spaces are not dilated. It is generally true that the distention of glomerular spaces and tubules is a very variable finding. It should be consistent and marked, if edema causes the anuria, by pressure on the tubular apparatus. Equally important is the fact that the gross swelling of the kidney may be negligible or absent in interstitial nephritis with anuria. The temporary restoration of diuresis after decapsulation therefore requires another explanation.

Hemoglobin Casts and Anuria: In interstitial nephritis associated with hemoglobinuria, as in black water fever or after blood transfusion, the anuria has been explained mechanically. This theory, advanced by Baker and Dodds,[2] assumes that hemoglobin is precipitated in the tubules by acid urine which contains a sodium chloride concentration exceeding 1 per cent. The hemoglobin is converted into hematin and is supposed to block the urinary outflow. The authors have shown experimentally that this

precipitation and the anuria can be prevented if the urine is kept alkaline. It is, however, questionable whether their experiments on rats, which were later confirmed on dogs, can be applied to human beings. Furthermore, the tubular dilatation is variable in degree and distention of Bowman's capsule may even be absent. In their experiments with repeated hemoglobin transfusions and acid diet in dogs DeGowin, *et al.*,[7] succeeded in producing hematin casts in the collecting tubules "so arranged as to block the tubules completely." The majority of their dogs, however, excreted a volume of urine which "continued to be fairly high until death occurred." Hence, the presence of hemoglobin casts does not prove that they actually cause urinary suppression by mechanical blockage. In this connection it is of interest to notice that Case 2 (reported above) showed seemingly complete blockage of collecting tubules with hemoglobin casts, and yet the urinary volume was restored to normal.

Although the possibility of mechanical blockage of descending tubules by hematin casts cannot be denied, it appears at least doubtful whether such a process can be extensive enough to cause anuria.

Circulatory Disturbances and Anuria: Disturbance of circulation has been cited as the cause of anuria. We have to distinguish between local (renal) and general impairment of circulation. Each may play an important part. Many patients with acute anuria following blood transfusion, burns, hepatic injuries, and so on, die under conditions resembling shock. Falling blood pressure, indicating the collapse of peripheral circulation, furnishes reasonable explanation for the reduced urinary output. Provided the kidney function is normal, one should under such circumstances expect a highly concentrated urine. It has, however, frequently been pointed out that isosthenuria or hyposthenuria is characteristic of this type of case and it has, therefore, been concluded that the impairment of renal function is the ultimate cause of oliguria. This assumption, in my opinion, is only partially correct. The mechanism may be interpreted as follows: diminished peripheral circulation results in reduced capillary pressure and reduced glomerular filtration. A diminished oxygen supply to the epithelial apparatus, on the other hand, causes reduction of their function. Hence, less water is reabsorbed. Thus, oliguria and decreased

concentration power from this point of view are to be looked upon as parallel phenomena, both resulting from insufficient peripheral circulation.

This explanation, however, does not apply to those cases in which there is no impairment of circulation. These cases (for instance Cases 1, 3 and 6, reported above) show normal or increased blood pressure during the period of marked oliguria with low specific gravity of the urine. One may think of locally (renal) impaired circulation, which may be brought about by increased intrarenal pressure, to be due to edema. One may also consider the possibility of vascular spasm. Hesse and Filatov [15] have given experimental evidence of arterial spasm in the kidney in hemolytic shock. The same theory is advanced to explain the anuria following liver injury (Furtwaengler,[9] and Pytel [28]). A satisfactory explanation has not as yet been given.

Renal Changes and Anuria: It is noteworthy that there is no consistence in regard to the evidence on which the various theories of the renal origin of anuria are based. Anuria of the isosthenuric or hyposthenuric type with a rise in non-protein nitrogen may be associated with various degrees and types of renal changes. Cellular infiltration, edema, hematin casts, tubular dilatation and epithelial degeneration may be present simultaneously, but any one of these processes may be absent. Thus, it seems more likely that these morphological changes are more of an accessory nature and that they are to be looked upon as a reflection of extrarenal disturbance not causing the anuria but accompanying it.

In fact, morphological changes in the kidney may be entirely absent in anuric uremia. It is not our purpose to discuss the various conditions in which "extrarenal uremia" with anuria occurs. If we intend, however, to evaluate the significance of structural changes in the kidney in regard to their function we must bear in mind that no parallelism can be established. Neither one of the above mentioned changes in the kidney fully explains the renal origin of anuria.

There is even uncertainty as to whether any of the functional disturbances necessarily indicates renal damage. The oliguria, if not caused by circulatory failure, may be due to what Lichtman and Sohval [21] called prerenal deviation of water. The hyposthenuria may be both renal and extrarenal in origin, as Nonnen-

bruch [25] and Weiser [30] pointed out. Function tests may reveal only slight impairment of function (Cooper [6]).

Hence, we conclude that sufficient evidence has not been presented to prove the renal origin of anuria and uremia in acute interstitial nephritis and associated conditions on the basis of morphological changes. Pure functional disturbances of circulation are more likely to be its cause.

Concept of Interstitial Nephritis

It is reasonable to conclude that acute interstitial nephritis represents an accessory local manifestation of a general reaction of the body to a toxic protein split product. More specifically, I regard it as a hyperergic reaction. The toxic substances, which I assume to be protein split products, may result in various injuries to parenchymatous organs. It may cause a shock-like condition and produce anuric uremia. If the kidney tissue is hypersensitive to this protein split product a non-specific hyperergic reaction takes place, the manifestation of which is the interstitial nephritis.

I have pointed out above that most authors discussing interstitial nephritis in infectious conditions interpret it as a hyperergic reaction to bacteria and their toxins. Although bacteria seem to play a most important rôle in the production of interstitial nephritis, in many cases they are not essential.

There seems to be sufficient evidence that acute interstitial nephritis can be produced experimentally by repeated injections of any non-bacterial antigen such as serum or egg white. Longcope,[23] who attempted to produce a prolonged anaphylactic shock in animals, observed marked diffuse or focal interstitial nephritis. Ahlström,[1] working with bacterial toxins and serum, specifically designates the interstitial nephritis as a non-specific allergic reaction of the kidney. The complete literature on this subject can be found in Horn's paper [16] on the experimental nephropathies.

Interstitial nephritis, on the other hand, is found to be accompanied by conditions we do not ordinarily associate with allergy, such as acute severe hemolysis, concomitant or anteceding liver damages, burns, and so on. It is not invariably present in such cases and if so varies considerably in degree. If it occurs, it indicates, in my opinion, that an allergic factor is involved. This

concept is in keeping with the interpretations given to any one of the various conditions in question. In fact, it is strongly supported by a number of theories and facts, some of which will be pointed out.

So-called hemolytic shock following blood transfusion with "compatible" blood may have characteristics resembling anaphylactic reaction (Bordley,[4] and Witts [32]). Urticarial rash, for instance, may appear immediately after transfusion. The hemolysis, though usually present, may be absent in fatal cases (Hancock [12]). That hemolysis is not an indispensable factor has been shown by Petroff and Bogomolova,[26] who experimentally reproduced an identical condition with plasma alone. The urinary suppression, in particular, does not parallel the hemolysis (Iljin [18]), but rather depends on protein split products liberated from hemolyzed red blood cells. It is the protein and its split products which may, though not in all cases, result in an allergic hyperergic reaction. The same is true of various conditions associated with severe hemolysis, such as black water fever which has frequently been interpreted as an allergic phenomenon.

Anuria in so-called hepatorenal syndrome is likewise believed to be the effect of foreign proteins or their split products which are either liberated from destroyed liver tissue or passing undetoxified from the intestine through the functionally impaired liver into the circulation (Boyce and McFetridge,[5] Helwig and Schutz,[14] Pytel,[28] Koch,[19] Rosenbaum,[29] and Wilensky and Colp [31]).

Thus, the common denominator for all conditions in which we encounter interstitial nephritis is the foreign protein or protein split product derived from bacteria, their toxins, destruction of cells, destruction of erythrocytes, or possibly inadequately assimilated protein absorbed through the intestine.

Its effect depends on its nature and the state of reaction of the body cells. In the first place, it may result in an acute or prolonged shock-like condition. Various purely degenerative lesions may be encountered in the kidney and the liver. Attention has largely been focused on regressive changes in the tubular epithelial cells of the kidney in severe hemoglobinuria. They are described as necrotizing nephroses, whereby excretion or reabsorption of hemoglobin may be a contributing factor to the degeneration

of epithelial cells. In fatal cases of so-called hepatorenal syndrome they are believed to be the result of the specific action of hepatogenic toxic substances. Focal necrosis in the liver and tubular degeneration in the kidney, however, are such common findings under such a multitude of circumstances that they hardly bear specific significance.

In the second place, foreign proteins and protein split products may act as an antigen. Permanent or periodic discharge will in time result in an allergic reaction, which may set forth inflammatory changes in various tissues (hyperergic reaction). The interstitial nephritis is the most prominent manifestation; interstitial hepatitis, myocarditis, pancreatitis and adrenalitis are less frequently encountered. Thus, I would not expect interstitial nephritis to appear at too early a date, an assumption that well coincides with actual observation. Kuczynski [20] reports an interesting case of scarlet fever in which death occurred as early as 2 days after onset of the rash. Although the kidneys were markedly edematous and revealed hyperemia of the cortex, and cellular interstitial infiltration was absent, the tubular epithelial cells showed degeneration.

In the cases of hepatorenal syndrome purely degenerative changes are noted if death occurs in 24 to 48 hours. Interstitial nephritis is observed in those instances in which 5 to 7 days elapse after the liver injury (operation) before the patient dies. The same apparently is true in fatalities following blood transfusions, and prompted Baker's [3] statement that edema and interstitial infiltration should be looked upon as a "late result."

It becomes clear from this point of view that oliguria or anuria and interstitial nephritis are coincident rather than causatively connected, both resulting from foreign protein or protein split products. Although they must not necessarily be present simultaneously, we are not surprised to find them frequently associated. Such coincidences, however, do not justify the separation of interstitial nephritis with hyposthenuric oliguria as a disease entity.

NOTE: I wish to acknowledge my indebtedness to my medical and surgical colleagues who have so kindly allowed me the free use of their clinical records.

Summary and Conclusions

1. Six cases of acute hematogenous interstitial nephritis are presented, all of which show more or less marked isosthenuric oliguria or anuria and a rise of non-protein nitrogen in the blood. Twelve other cases of interstitial nephritis, which were found incidentally at autopsy, are included.

2. The morphological characteristics of this lesion are described. It is emphasized that even in the early stage the interstitial exudate contains plasma cells, lymphocytes, eosinophils and monocytes, in addition to polymorphonuclear leukocytes. A distinction between focal and diffuse interstitial nephritis should not be made.

3. The conditions causing interstitial nephritis are listed. In addition to the infectious diseases and septicemia, it is found to follow conditions associated with hemolysis, in particular blood transfusion with incompatible blood. It is also found in the hepatorenal syndrome with infectious and non-infectious liver injuries.

4. The correlation of functional disturbances with interstitial nephritis is discussed. It is concluded that the anuria does not result from renal edema by pressure on the tubular apparatus, neither is it caused by blockage of tubules if associated with hemoglobinuria. General or local renal circulatory disturbances are held to be the most likely cause of oliguria and lack of concentration power.

5. Hematogenous interstitial nephritis is regarded as an allergic hyperergic reaction to foreign proteins or protein split products coincidental rather than causatively connected with hyposthenuric oliguria and anuric uremia.

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THE PHARYNGEAL PITUITARY GLAND *

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Accessory or aberrant nodules of the endocrine tissues are not an infrequent finding. Notable examples are the lateral aberrant thyroid, the lingual thyroid, and adrenal cortical tissue beneath the capsule of the kidney. In most instances the small masses are found along the pathway of developmental migration of the main organ.

The anterior lobe of the pituitary gland is derived from an epithelial evagination of the roof of the posterior nasopharynx, known as Rathke's pouch. This mass of epithelial cells loses its attachment to the pharynx, migrates through the tissue which later becomes the body of the sphenoid bone, and comes to rest in the anlage of the sella turcica. Small masses of pituitary tissue may occasionally be found in the body of the sphenoid bone but according to the investigations of Haberfeld [1] and Christeller [2] there always remains a small piece of typical or atypical pituitary tissue in the pharyngeal mucosa that has been designated as the pharyngeal pituitary gland.

METHODS

Material from 54 autopsies at the New York Hospital during the period from July 1936 to May 1937 was used. In order to avoid autolytic changes only those cases in which the autopsy was performed a few hours after death were chosen for study. Otherwise there was no selection of the specimens.

The base of the skull was exposed by removal of the calvarium and brain. A coronal cut just anterior to the optic groove was made with a chisel through the body of the sphenoid bone and the bony nasal septum into the posterior nasopharynx. From each lateral extremity of this incision sawcuts through the thickness of the base of the skull were extended posteriorly and brought to taper in the occipital bone at a point near the foramen magnum.

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After fixation in 6 per cent formaldehyde the pituitary gland was dissected free, weighed and measured, and then cut into four horizontal blocks. One paraffin section from each block was stained with Mallory's aniline blue collagen stain. The mucosa and periosteum covering the vomer were stripped from the bone as far as the junction of the vomer and the sphenoid. The firm fibrous tissue and vascular channels that enter the periosteum at the vomerosphenoidal articulation were cut across and the firmly adherent periosteum was dissected from the remainder of the nasopharyngeal surface of the vomer. A sagittal block from the midline, centered on the vomerosphenoidal articulation, approximately 3 mm. in lateral dimension and 15 to 25 mm. in anteroposterior dimension, was prepared and embedded in paraffin. Alternate successive groups of 5 and 10 sections each were saved and discarded respectively until the entire block was cut. The first section of each group of 5 was stained with hematoxylin and eosin. The additional sections were used for staining with Mallory's aniline blue collagen stain, Krause's differential stain, and van Gieson's method. A total of over 8800 sections was mounted.

The greatest anteroposterior and cephalocaudal dimensions were determined with an ocular micrometer. The greatest lateral dimension was computed from the number of sections in which the pharyngeal pituitary appeared.

In this paper the term pituitary gland will be used in the ordinary sense to designate the structure contained in the sella turcica, and the term pharyngeal pituitary gland to designate the pituitary-like structure located in the mucosa of the nasopharynx.

Frequency, Location, Shape and Size

The pharyngeal pituitary gland was found in 51 of the 54 cases studied. It was most constantly located in the midline deep in the mucosa or in the periosteum beneath or near the vomerosphenoidal articulation (Fig. 1). It occurred most frequently as a single, well circumscribed and encapsulated structure. In a few instances irregular cords or islands of cells extended into the surrounding tissue. The general shape was that of a flattened prolate spheroid.

Haberfeld [1] studied the pharyngeal pituitary in 51 cases and concluded that most of the growth of the gland occurred in the fetus and during the first few months of life, and that there was little or

no growth thereafter. A study of the size of the pharyngeal pituitary gland in the present series confirmed this conclusion (Table I). An analysis of variance of the age of the individuals (decades) and the size (sum of the three dimensions) of the pharyngeal

TABLE I

Sum of the Three Dimensions (Millimeters) of the Pharyngeal Pituitaries of Individuals in Cases Studied in Relation to Age

Less than 1 mo.	1 mo.–1 yr.	1–10 yrs.	11–20 yrs.	21–30 yrs.	31–40 yrs.	41–50 yrs.	51–60 yrs.	Over 61 yrs.
0.53	3.01	1.38	1.97	1.31	1.05	1.17	0.67	1.84
0.74	5.36	2.51	2.14	1.91	3.69	2.41	2.41	2.64
1.23	6.93	3.87	4.35	2.06	4.19	3.66	2.73	4.73
1.87			4.71	3.81	5.67	3.82	3.15	
1.98			5.48	6.52	6.25	3.89	3.95	
3.14			8.12		6.55	4.75	4.78	
					7.12	5.33	4.90	
							5.32	
							5.43	
							5.46	
							6.44	

pituitary showed that there was as much variation of size within the decades as between the decades (Table II). The lack of progressive growth of the pharyngeal pituitary is in contrast with the increase in size of the pituitary gland which is rapid in the first

TABLE II

Analysis of Variance of Sum of Three Dimensions of Pharyngeal Pituitaries Studied and Age by Decades

Source of Variation	Degrees freedom	Total squares	Mean square
Total	50	187.14	3.74
Between	8	35.96	4.49
Within	42	151.18	3.60

F = 1.25 — not significant.

decade and progresses gradually through puberty into adult life.

The largest pharyngeal pituitary gland observed in this series occurred in a girl 15 years of age and measured 6.62 mm. in length, 1.15 mm. in width, and 0.35 mm. in depth. The smallest gland was in a newborn infant and measured 0.22 mm. in length, 0.21 mm. in width, and 0.10 mm. in depth.

Histological Features

The pharyngeal pituitary glands were composed essentially of undifferentiated epithelial cells and differentiated cells similar to those in the anterior lobe of the pituitary gland.

Undifferentiated epithelium was present in 32 of the 51 cases. It was usually of the transitional type but in 1 instance there were definite intercellular bridges. Keratinization and keratin granules were not observed. The undifferentiated cells were arranged in small nests with an indefinite basal layer. The relative amount of undifferentiated epithelium in each case in relation to age is shown in Table III.

Table III

Relative Amounts of Undifferentiated Epithelium in Pharyngeal Pituitaries with Ages in Years of Individuals

None		One plus	Two plus	Three plus	Four plus
1	12	38	14	15	1
1	22	52	17	37	1
1	22	55	20	45	16
1	30	57	32	46	24
1	30	69	47	55	34
1	40		50	58	35
1	40		53	59	41
1	51		59	80	49
4	54		59		55
6			72		

Statistical evaluation of these figures by the method of analysis of variance showed that there was greater variation within the groups than between the groups. The insignificant correlation between the amount of epithelium and the age of the patient indicates that there is no progressive differentiation of the cells as is found in other functional organs.

In 3 cases there was cyst formation within the transitional epithelium and slight infiltration with polymorphonuclear leukocytes. In 10 cases there were glandular acini lined by columnar or cuboidal cells. The lumens contained an acidophilic homogeneous substance. In 7 of the 10 cases the acini were associated with nests of transitional epithelium.

The differentiated tissue in the pharyngeal pituitary had the same histological appearance as that in the pituitary gland (Fig. 2),

but there were conspicuous quantitative differences. An approximation of the relative numbers of acidophilic and basophilic cells in the pharyngeal pituitary is shown in Table IV.

With the exception of the acidophilic cells in 6 cases there was a conspicuous deficiency of basophilic and acidophilic cells. In 17 and 18 cases the acidophilic and basophilic cells respectively were entirely absent, and in 13 both were absent. In 7 of the 13 instances in which chromophilic cells were absent, chromophobic cells were also absent. Thus, in 25 per cent of cases there were no chromophilic cells and in 35 per cent either the acidophilic or basophilic cells were absent. Even when chromophilic cells were present they were few in number and constituted less than 1 per cent

TABLE IV

Relative Numbers of Chromophilic Cells in Pharyngeal Pituitaries

	Acidophilic cells		Basophilic cells	
None		17		18
One plus	11		24	
Two plus	15		8	
Three plus	2		1	
Four plus	6		0	
Total positive		34		33
Total		51		51

of all cells. The relative deficiency of chromophilic cells and the small size of the entire gland render it unlikely that the pharyngeal pituitary contributes any significant part to pituitary function.

Colloid was frequently associated with the chromophilic cells and was present as a conspicuous element in 11 cases. This colloid was for the most part fuchsinophilic in the classification of Kraus [3] and probably represented degenerating cells. In 3 of the 11 cases there was also conspicuous colloid in the pituitary gland but the condition in the two locations was not closely correlated.

The basophilic cells were vacuolated in 2 cases and the eosinophilic cells in 1 case. Vacuolization of the basophils is usually accepted as an index of function and upon this basis secretory activity must be accepted. The analogous cells in the pituitary were in all 3 instances vacuolated.

The interstitial tissue and vascular supply of the pharyngeal pituitary were essentially the same as in the pituitary. There were

delicate strands of connective tissue and numerous thin walled capillaries. Haberfeld [1] reported a progressive increase in the stroma with advancing age, but this was not apparent in the present series, nor was it noted in the cases studied by Christeller.[2]

In 1 case the pharyngeal pituitary was associated with a small lymph node. In most cases there were numerous myelinated nerves and large vascular sinusoids in the surrounding tissue.

In 3 cases, individuals 1, 14 and 24 years old respectively, the pharyngeal pituitary gland was located immediately beneath the epithelial cells of the pharyngeal mucosa, and in an additional 2 cases, a stillborn infant and a 69 year old male, there was actual union of the hypophyseal and mucosal cells (Fig. 3).

Special Cases

Of particular interest were a number of cases in which the pituitary gland showed pathological changes: (1) a female, 34 years old, who died of cerebral hemorrhage 16 hours postpartum at term; (2) a boy, 16 years old, with an adamantinoma of the sellar region and apparently complete compression atrophy of the pituitary; (3) a girl, 12 years old, with Addison's disease and absence of basophilic cells in the anterior lobe of the pituitary; and (4) a male, 32 years old, with widespread metastases from a teratoma of the testis.

The cases of pregnancy and teratoma of the testis may be considered together. In a physiopathological analysis of diseases of the pituitary Erdheim [4] concluded that all conditions associated with urinary excretion of prolan result in the same alterations in the pituitary gland, namely the appearance of the so-called "pregnancy cell." Pregnancy cells [5] are about the same general size or slightly smaller than acidophilic cells. They tend to a columnar shape and palisade arrangement, are vacuolated at the ends, have a stringy reticulated cytoplasm and contain a few acidophilic granules. In the pharyngeal pituitary from the postpartum female transitional epithelium (Fig. 4) was the only cellular type present. It should be pointed out that the epithelial cells in this case are larger and the cytoplasm is less chromatic than in any other case. In the patient with a teratoma of the testis there were abundant acidophilic cells in the pharyngeal pituitary. The acidophilic cells were moderately well granulated and could not be identified

as "pregnancy cells." This patient was known to be excreting large quantities of prolan and the failure of either hypertrophy or the appearance of pregnancy cells in the pharyngeal pituitary is strong evidence of lack of response to an adequate stimulus. The significance of the abundant acidophilic cells associated with teratoma of the testis is difficult to evaluate because in 5 other cases the acidophilic cells were conspicuous and not related to an endocrine disturbance. Christeller [2] reported a case of Froehlich's syndrome associated with destruction of the pituitary and abundant eosinophilic cells in the pharyngeal pituitary. In the 5 pharyngeal pituitaries from pregnant females studied by Haberfeld [1] there was no distinctive feature.

In the patient with an adamantinoma of the hypophyseal stalk and apparent destruction of the entire pituitary gland the pharyngeal pituitary was again composed of undifferentiated epithelium and no deductions on possible compensatory hypertrophy are possible. Female distribution of hair, general adiposity and hypoplasia of the genitalia in this 17 year old boy support the diagnosis of disturbed pituitary function. Christeller [2] reported 2 cases of neoplastic compression of the pituitary in which the pharyngeal pituitary was composed entirely of undifferentiated epithelium.

Kraus [6] first noted that in Addison's disease there is a conspicuous decrease or absence of basophilic cells in the anterior lobe of the pituitary. In the 1 case of Addison's disease in this series basophilic cells were entirely absent in the pituitary but in the pharyngeal pituitary there were a very few definite basophilic cells with vacuoles. The presence of these basophilic cells is further evidence that cells in the pharyngeal pituitary of similar morphological appearance to those in the pituitary do not react to the same stimuli.

Discussion

A critical evaluation of the morphological findings in terms of physiological function is difficult because of the limited number of observations of the pharyngeal pituitary in examples of known disturbances of the pituitary gland. The lack of significant change in the pharyngeal pituitary in 5 pregnant females reported by Haberfeld [1] and the one in this series indicates that the cells do not respond to the altered hormonal conditions of pregnancy. The

failure of compensatory hypertrophy in the 2 cases of neoplastic compression of the pituitary observed by Christeller [2] and the 1 similar case in this series is further evidence of an inability to respond to an adequate stimulus. Finally, there is no evidence of progressive growth and differentiation that is observed in all other endocrine glands.

The case reported by Christeller [2] and 1 in the present series in which there are conspicuous eosinophilic cells in the pharyngeal pituitary associated with Froehlich's syndrome and teratoma of the testis, respectively, indicate possible physiological activity. There is also the minor histological evidence of function as shown by occasional vacuolization of the chromophilic cells.

Summary and Conclusions

A small mass of typical or atypical pituitary tissue was found in the pharyngeal mucosa in 51 of 54 unselected cases examined. The differentiated cells in the pharyngeal pituitary gland are histologically identical with those in the anterior lobe of the pituitary gland but there are relatively few chromophilic cells.

Under normal conditions of growth and activity it is unlikely that the pharyngeal pituitary gland contributes any significant physiological function, but in some cases of altered structure or activity of the pituitary gland it cannot be denied that the pharyngeal pituitary gland may undergo structural alterations and serve as an endocrine organ.

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DESCRIPTION OF PLATE

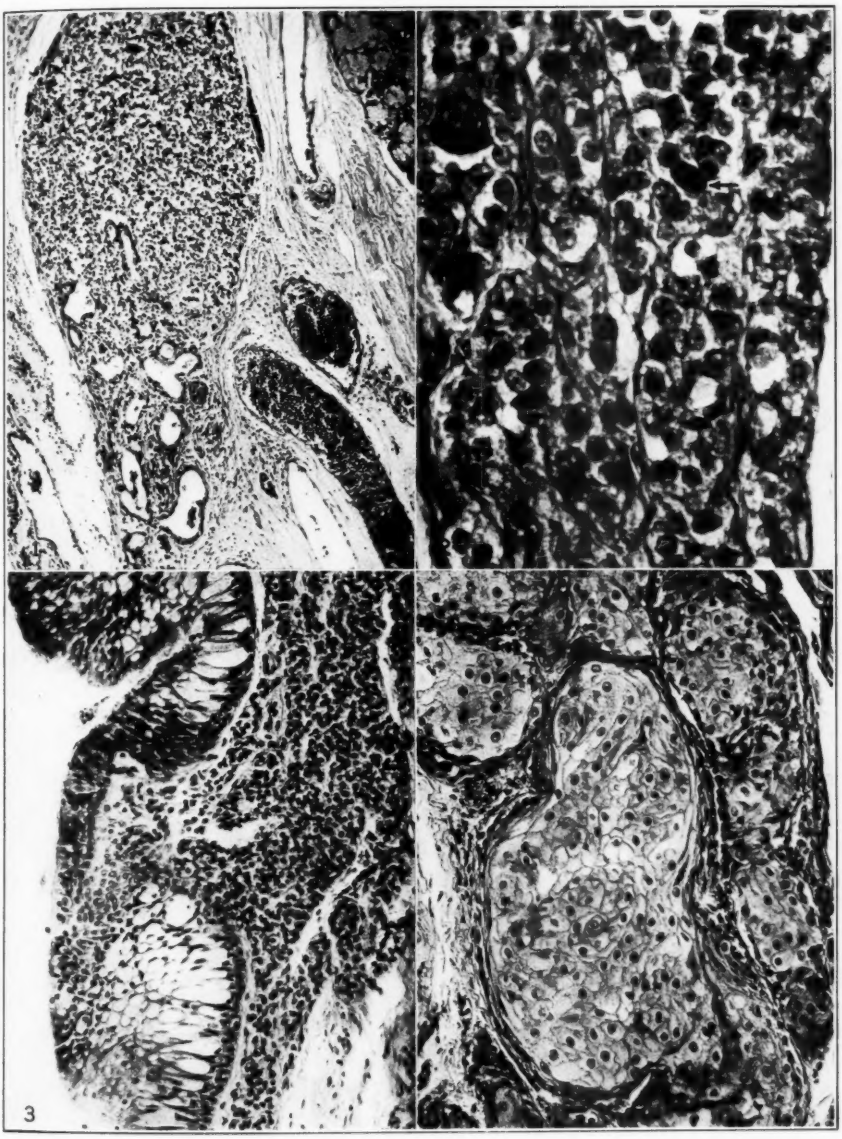
PLATE 145

FIG. 1. A pharyngeal pituitary gland composed of differentiated cells and a few glandular acini. Note the mucosal glands of the pharynx at one side and the large vascular spaces in the surrounding fibrous tissue.

FIG. 2. A high power microphotograph to show the appearance of the differentiated cells of the pharyngeal pituitary. The arrow points to an acidophilic cell.

FIG. 3. A microphotograph to show union of the pharyngeal pituitary with the epithelial cells of the mucosa of the pharynx.

FIG. 4. Swollen transitional epithelium in the pharyngeal pituitary associated with pregnancy.



Melchionna and Moore Pharyngeal Pituitary Gland

DIFFERENCES BETWEEN CASTRATION CELLS AND THYROIDECTOMY CELLS OF THE PITUITARY OF THE RAT IN RESPONSE TO THE ADMINISTRATION OF ESTRONE AND THYROID EXTRACT *

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In previous experiments I have made attempts to identify the histological types of cells in the pituitary which produce the various pituitary hormones. Histological differences have been described between the cells in the rat's pituitary which react to thyroidectomy and the cells which react to castration [1, 2]; differences have been described in the manner in which the adrenals react to these two operations [3, 4]; variations in the weight of the pituitary after these operations have been recorded [2]; and I have suggested that thyroidectomy cells and castration cells probably produce different hormones,[5] and that the adrenocorticotropic hormone is unrelated either to thyroidectomy cells or to castration cells.[4] These structural and functional differences have led me to regard these cells as having more differences than similarities. In fact, thyroidectomy cells in histological appearance in some ways seem more like chromophobes than basophils, in so far as the cytoplasm stains with difficulty and contains only fine granules.[2]

On the other hand, some investigators have regarded castration cells and thyroidectomy cells as identical. Severinghaus, Smelser and Clark [6] described the histological changes in 9 thyroidectomized rats as "typical castration cells" and said that the "basophiles of the thyroidectomized rats are similar to those of castrate and thyroid-treated rats." The fact that the testes do not atrophy in thyroidectomized rats [3] indicates that thyroidectomy cells do not develop in the same manner as castration cells because of a lack of hormone from the gonads.

Reference has been previously made [3] to the experiments published by a number of investigators who have found that the pituitaries of castrated animals contain and secrete an excess of

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gonadotropic hormones. If castration cells are the same as thyroidectomy cells one might expect to find a simultaneous secretion of thyrotropic hormone by the castration cells, but in the literature the weight of evidence is against any increased thyroid activity in the castrated animal. Furthermore, the pituitary of the thyroidectomized animal, which contains an abundance of thyrotropic hormone,[5] contains a decreased amount of gonadotropic hormone in the female, while no data in the literature have been found for the male. Severinghaus [7] writes: "We are at a loss to explain the failure of glands (pituitary) of either the thyroidectomized or the thyroid treated animals to show increased gonadotropic potency by the implant test. In both instances there is a marked increase in basophilia comparable structurally to the basophilic changes after castration, which do not show increased potency. In the writer's opinion, this discrepancy constitutes a true stumbling block to those who have hopes of correlating structural changes with function, and some satisfactory explanation of the discrepancies must be forthcoming." To me there are no discrepancies and no stumbling blocks if one grants that thyroidectomy cells are not identical with castration cells in structure and produce different secretory products. On the basis of this conception the complete dissociation between formation of thyrotropic hormone and gonadotropic hormone determined by implant tests for potency is satisfactorily explained.

Recently Nelson and Hickman [8] have opposed some of my conclusions because of the results of their experiments dealing with estrone injections into thyroidectomized rats. They state: "The effectiveness of oestrone in preventing and correcting the changes which occur in the hypophysis following thyroidectomy is similar to its action on the changes that follow castration and appears to be evidence against the idea that the basophiles which react to the 2 operations represent 2 different cell types." Severinghaus [9] in a review article writes that he and Smelser in some unpublished experiments find that "the injection of 5 r.u. of progynon daily into thyroidectomized female rats prevented vacuolation of pituitary basophiles over 50 days." Previously, however, Hohlweg and Junkmann [10] had found that progynon (estrogenic) injections prevented the development of castration cells but not thyroidectomy cells.

It would seem to me that the conclusions drawn by Nelson and Hickman would hold only if it were proved that estrone had a selective action on the basophils that develop into castration cells and on no other cell. In the dosage they used (40 R.U. daily) no diffuse effects would be anticipated, but in the voluminous literature on the effect of estrone, most workers are agreed that repeated estrone injections in large doses degranulate all granular cells of the pituitary, including acidophils, producing finally a chromophobic pituitary. Hence there is no reason why thyroidectomy cells should not be degranulated, if sufficient dosage is used, even if they represent a different type of cell from that which gives rise to the castration cell.

The following experiments * were carried out in order to gain further evidence of similarity or difference in the reaction of the pituitary after castration and after thyroidectomy to the administration of estrogenic hormone and thyroid extract.

Methods

White rats from an inbred colony maintained in this laboratory for 5 years were operated upon at 5 weeks of age and killed 5 weeks later. The pituitaries were fixed immediately in Helly's fluid and stained with Mallory's aniline blue collagen stain. The pituitaries of several different rats subjected to different types of experiments were prepared in the same way and mounted on the same slide as a control for staining. Ninety-three rats were studied as follows: 7 males and 6 females gonadectomized and receiving no treatment; 6 males and 6 females thyroidectomized and receiving no treatment; 7 males and 7 females gonadectomized and injected with estrone (theelin in oil, Parke, Davis & Company); 15 males and 13 females thyroidectomized and injected with estrone; 2 males and 2 females thyroidectomized and fed desiccated thyroid extract (U.S.P., Abbott Laboratories) in a dosage known to prevent the development of thyroidectomy cells; 4 males and 3 females gonadectomized and fed thyroid extract in the same or larger dosage; 4 males and 3 females not operated upon and untreated as controls for age and sex; and 5 males and 3 females not operated upon and injected with estrone.

* The results were read in brief before the American Association of Pathologists and Bacteriologists, May 3, 1938, *Am. J. Path.*, 1938, **14**, 650–651.

Results

Five weeks after operation the histological differences between castration and thyroidectomy cells are much more obvious than at later periods. The castration cells have not yet developed their signet ring appearance and so contain no hyaline material in a vacuolated space as occurs in later stages. They appear as numerous enlarged and uniformly granulated basophils comprising about 50 per cent of the anterior pituitary, and the acidophils are not noticeably altered. On the other hand, after thyroidectomy the pituitary has attained the maximum change at 5 weeks, the predominating cells being thyroidectomy cells containing large amounts of intracellular hyaline, with very fine, poorly staining granules in the remaining portion of the cytoplasm. Nearly all the acidophils have disappeared.

In varying the dosage of estrone injected so as to determine the dosage effective for suppressing castration cells, in the first experiments a few rats were given an ineffective dosage (see Tables I and II). In a few of the earlier experiments treatment was not begun until 2 or 3 weeks had elapsed after operation and this was found not to be a suitable method. In all other experiments estrone or thyroid extract was administered 6 times a week from the day of the operation to the day of killing the rat. As body growth is inhibited by thyroidectomy, the dosage stated really represents a larger dose per gram of body weight in the case of the thyroidectomized than in the gonadectomized rats, which tend to be heavier than normal.

The microscopic sections were first examined and classified without knowledge of the nature of the experiment. Without exception all pituitaries of thyroidectomized rats were recognized as such whether the rats were untreated or had been injected with estrone. In 6 thyroidectomized males injected with a total of 1200, 1450, 2320, 2900, 2900 and 4350 international units of estrone, thyroidectomy cells were present as the predominating cell. After the largest doses only, were thyroidectomy cells slightly reduced in number. All 5 gonadectomized males injected with 1450, 2320, 2900, 3360 and 4350 international units showed complete suppression of castration cells so that a castration effect was unrecognizable. In 7 thyroidectomized females injected with a total of 595, 615, 615, 1160, 1500, 2900 and 2900 international units,

TABLE I

Data on Female Rats

Number of rats	Operation	Treatment. Total dosage in postoperative period	Period over which treatment administered	Histological appearance of pituitary
3	None	None	..	Normal pituitary
1	"	240 I.U. estrone	Last 2 weeks	No conspicuous changes
1	"	950 " "	" 3 "	" " "
1	"	635 " "	" 5 "	" " "
6	Gonadectomized	None	..	Typical castration changes
1	"	240 I.U. estrone	Last 2 weeks	Very few castration cells
1	"	950 " "	" 3 "	Castration cells reduced
1	"	635 " "	" 5 "	No castration cells
1	"	1160 " "	" 5 "	" " "
1	"	1500 " "	" 5 "	" " "
2	"	2900 " "	" 5 "	" " "
6	Thyroidectomized	None	..	Typical thyroidectomy changes
3	"	260 I.U. estrone	Last 2 weeks	" " "
3	"	750 " "	" 3 "	" " "
1	"	595 " "	" 5 "	" " "
2	"	615 " "	" 5 "	" " "
1	"	1160 " "	" 5 "	" " "
1	"	1500 " "	" 5 "	" " "
2	"	2900 " "	" 5 "	" " "
1	Thyroidectomized	0.928 gm. thyroid extract	Last 5 weeks	Normal pituitary
1	"	1.151 " " "	" 5 "	" "
1	Gonadectomized	0.957 gm. thyroid extract	Last 5 weeks	Typical castration changes
1	"	1.677 " " "	" 5 "	" " "
1	"	1.972 " " "	" 5 "	" " "

TABLE II

Data on Male Rats

Number of rats	Operation	Treatment. Total dosage in postoperative period	Period over which treatment administered	Histological appearance of pituitary
4	None	None	..	Normal pituitary
1	"	240 I.U. estrone	Last 2 weeks	No conspicuous changes
1	"	850 " "	" 3 "	" " "
1	"	900 " "	" 3 "	" " "
1	"	580 " "	" 5 "	" " "
1	"	2800 " "	" 5 "	" " "
7	Gonadectomized	None	..	Typical castration changes
1	"	240 I.U. estrone	Last 2 weeks	" " "
1	"	580 " "	" 5 "	Fewer castration cells
1	"	1450 " "	" 5 "	Castration cells degranulated
1	"	2320 " "	" 5 "	No castration effect
1	"	2900 " "	" 5 "	" " "
1	"	3360 " "	" 5 "	" " "
1	"	4350 " "	" 5 "	" " "
6	Thyroidectomized	None	..	Typical thyroidectomy changes
1	"	220 I.U. estrone	Last 2 weeks	" " "
2	"	260 " "	" 2 "	" " "
3	"	750 " "	" 3 "	" " "
3	"	580 " "	" 5 "	" " "
1	"	1200 " "	" 5 "	" " "
1	"	1450 " "	" 5 "	" " "
1	"	2320 " "	" 5 "	" " "
2	"	2900 " "	" 5 "	" " "
1	"	4350 " "	" 5 "	" " "
1	Thyroidectomized	0.957 gm. thyroid extract	Last 5 weeks	Normal pituitary
1	"	1.638 " " "	" 5 "	" "
2	Gonadectomized	0.957 gm. thyroid extract	Last 5 weeks	Typical castration changes
1	"	1.639 " " "	" 5 "	" " "
1	"	2.389 " " "	" 5 "	" " "

thyroidectomy cells were present in all pituitaries, though slightly reduced in number with the largest dosage, while all 5 gonadectomized females injected with 635, 1160, 1500, 2900 and 2900 units showed no castration cells and were unrecognizable as pituitaries from castrated animals.

In 4 gonadectomized males fed a total of 0.957, 0.957, 1.639 and 2.389 gm. of thyroid extract, the castration cells were not affected in the slightest, while 2 male thyroidectomized rats fed 0.957 and 1.638 gm. showed no thyroidectomy cells. In 3 gonadectomized females fed 0.957, 1.677 and 1.972 gm. of thyroid extract castration cells were not affected, while 2 thyroidectomized females fed 0.928 and 1.151 gm. of thyroid extract showed complete suppression of thyroidectomy cells. Figures 1 to 4 illustrate typical examples of pituitaries in each category. Tables I and II indicate the number of rats and the dosage used.

In the thyroidectomized rats the effect of estrone was obvious in its characteristic influence on the gonads. After large doses the testes were reduced to minute organs comparable to the effect of hypophysectomy because degranulation of the basophils which produce gonadotropic hormone is caused by estrone, and synchronous with this is the cessation of secretion of gonadotropic hormone, as determined by implantation experiments. In the thyroidectomized rats treated with estrone there was an increase in number of chromophobes, just as occurs in normal rats after estrone administration. This chromophobe increase gave the pituitaries of the treated thyroidectomized rats a slightly different histological pattern from that in the untreated thyroidectomized rats. Complete thyroidectomy was evidenced by marked inhibition of growth of the kidney, the short, plump external appearance of a dwarfed rat, and the characteristic histological appearance and gross enlargement and engorgement of the pituitary. The dosage used in most of these experiments enumerated above was much greater than that used by Nelson and Hickman, although small doses likewise had no effect on the thyroidectomized rats used in the preliminary experiments.

Discussion

In any normal pituitary there are great variations in the histological characteristics of the basophils. The conventional explana-

tion of this is that the different appearances represent different phases of secretory activity. It is not unreasonable or contrary to evidence to assume as a hypothesis that some of these variations of staining and degree of granularity really indicate that there are different varieties of basophilic cells producing different hormones. Granting this as a possibility, it would be conceivable that under normal conditions basophilic cells forming different hormones cannot be distinguished from each other on histological grounds, but that when a peripheral endocrine organ is ablated, and the pituitary cell which affects that peripheral organ reacts to the ablation, then different varieties of basophils can be dissociated. It would be difficult to determine with certainty from what original cell thyroidectomy cells are derived, that is, whether they are formed from a precursor chromophobe, or whether a basophil of a single type can differentiate in different directions to a castration cell and to a thyroidectomy cell. To some histologists the conception of more than one type of basophil seems to be a violation of fundamental principles, but to me it is even more difficult to accept that merely two types of secretory cells (one acidophilic and one basophilic) produce the numerous hormone effects that can be concretely demonstrated. Especially is this so when one realizes that the hormone effects need not occur synchronously but can be dissociated from each other. In any case, whatever may be the origin of the thyroidectomy cells, after they have developed they appear to be a different type of cell from the castration cell, structurally and functionally.

From what we know of the reciprocal relations between the pituitary and the peripheral endocrine organs we would expect the results described above. For instance, the pituitary producing the thyrotropic hormone stimulates the thyroid to secrete thyroid hormone, which in turn acts upon the pituitary, inhibiting its production of thyrotropic hormone, as has been determined by implantation experiments (Hohlweg and Junkmann [10]). In consequence of this the thyroid stops secreting its hormone. As a result of this, the inhibiting effect upon the pituitary is removed and it again resumes secretion of the thyrotropic principle. If the thyroid is ablated, the thyroidectomy cell that reacts in the pituitary is presumably the cell in the pituitary that is producing the thyrotropic hormone, and it would be expected that only the pres-

ence of the hormone secreted by the thyroid gland, and not estrone, would prevent the development of this cell and maintain a normal cellular pattern in the pituitary.

Estrone in large doses is well known to have a diffuse effect. It causes degranulation of basophils in both males and females and through this effect alters the structure of the gonads in both sexes. It retards body growth and since this is accompanied by degranulation of the acidophils, it probably produces the effect on growth by lessening the production of growth hormone by the acidophils. Consequently in large doses one would anticipate that estrone would affect the production by the pituitary of thyrotropic hormone and other hormones. Some of the doses used in these experiments were large enough to produce some of these diffuse effects, and yet the thyroidectomy cells were not prevented from developing.

Summary and Conclusions

Rats were operated upon at 5 weeks of age and killed 5 weeks later. Forty-four were thyroidectomized and 34 were castrated. In each group some were injected with estrone, some were fed thyroid extract, and some were untreated.

The lack of effect on thyroidectomy cells of estrone injected in a dosage greater than adequate to suppress castration cells, and the failure of castration cells to respond to thyroid extract in doses greater than required to suppress thyroidectomy cells indicate that thyroidectomy cells probably are structurally and functionally different cells from castration cells, whatever may be their derivation.

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DESCRIPTION OF PLATE

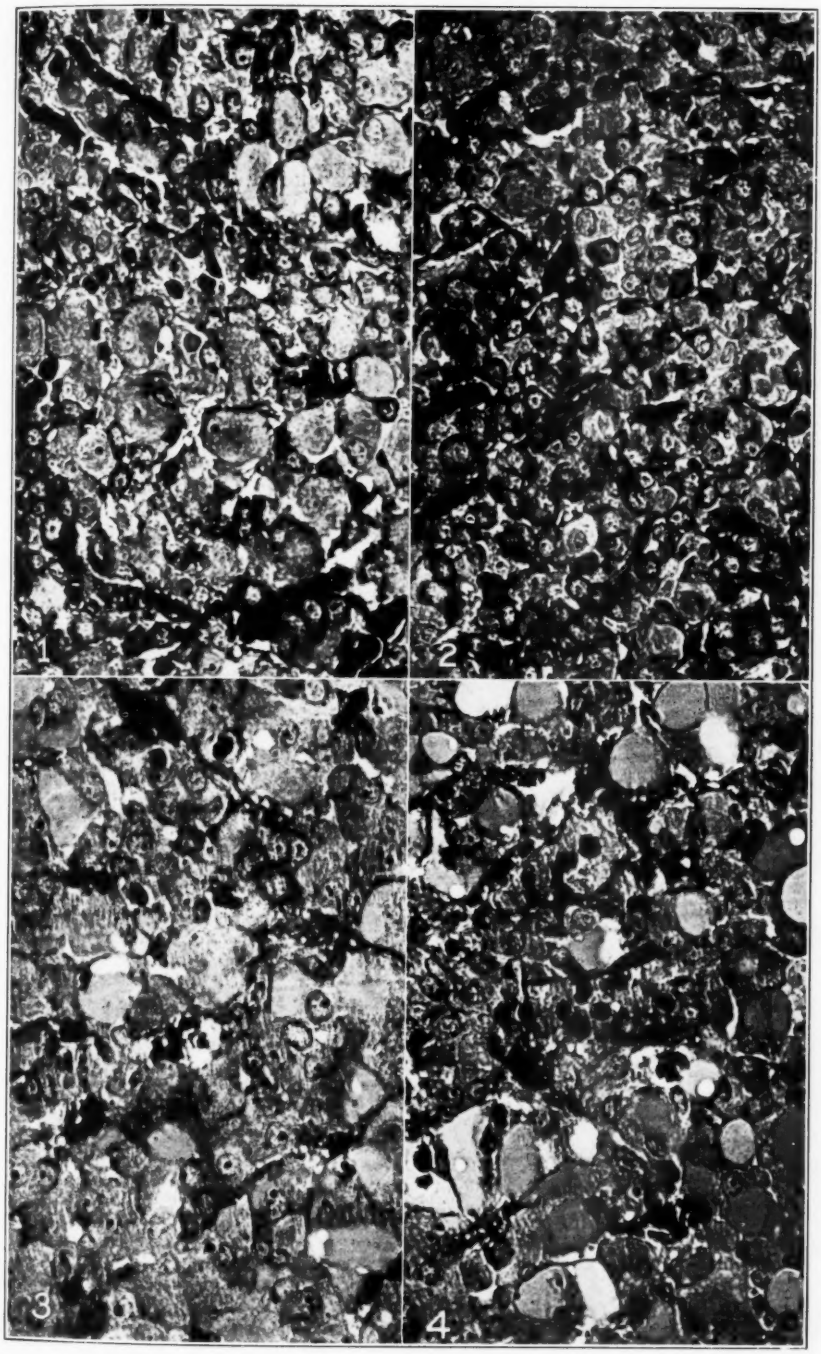
PLATE 146

FIG. 1. Male rat (12–S–3) castrated and receiving no treatment. Killed 5 weeks after operation. Typical castration effect, consisting of increased number and size of basophils. Acidophils normal. × 523.

FIG. 2. Male rat (12–S–1), litter-mate of preceding rat, injected with a total dose of 2320 I. U. estrone for 5 weeks after operation. No castration cells present. × 523.

FIG. 3. Male rat (12–S–4), litter-mate of preceding rat, thyroidectomized and receiving no treatment. Killed 5 weeks after operation. Typical thyroidectomy effect, consisting of marked loss of acidophils and development of thyroidectomy cells containing intracellular hyaline. × 523.

FIG. 4. Male rat (12–S–2), litter-mate of preceding rat, thyroidectomized and injected with a total dosage of 2320 I. U. estrone for 5 weeks after operation. Typical thyroidectomy cells abundant and loss of acidophils apparent. × 523.



Zeckwer

Castration Cells and Thyroidectomy Cells

HISTOLOGICAL VARIATIONS IN AUTONOMIC GANGLIA AND GANGLION CELLS ASSOCIATED WITH AGE AND DISEASE *

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Histological variations in autonomic ganglia and ganglion cells have been described by a number of investigators. Some have regarded the more marked changes as representing pathological lesions; others have regarded all the observed variations as representing structural changes falling within the normal range of variability. Most of the studies of which the results have been published have been carried out on preparations of ganglia of the sympathetic trunks and prevertebral plexuses obtained at autopsies following death due to widely differing causes and within wide age limits; some have been on preparations of sympathetic ganglia removed in the surgical treatment of certain diseases. The studies carried out on material of the latter type have revealed no specific histopathological changes in the ganglia which could be correlated with the disease in question. The histological variations observed in such material fall into the same general categories as those observed in preparations of ganglia obtained from apparently normal individuals and individuals with other diseases. Certain investigators, notably Craig and Kernohan,[1] consequently have advanced the opinion that most of the histological changes observed in preparations of autonomic ganglia can be explained most satisfactorily on the basis of advancing age.

Some of the histological variations observable in preparations of autonomic ganglia undoubtedly are correlated with the ages of the subjects. Others probably are associated with disease either as causative factors or accompaniments. Regardless of the specific relationships of lesions of the autonomic ganglia or ganglion cells to a disease process with which they are associated, the functional modifications associated with them may play a significant rôle in the progress of the disease and its sequelae. The establishment of norms for human autonomic ganglia and ganglion cells in the

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several age groups, consequently, would be desirable, but, on the basis of our present knowledge, such an undertaking must be regarded as hazardous.

Materials and Methods

The present study is based mainly on preparations of ganglia of the sympathetic trunks and the celiac plexus obtained in an extensive series of autopsies following death at ages ranging from 5 weeks to 78 years. The cases have not been selected with reference to disease, but the causes of death vary within a wide range. Preparations of sympathetic ganglia removed in the surgical treatment of disease in approximately 50 patients, ranging in age from 6 to 71 years, also have been available for study.

Most of the material has been fixed in 10 per cent formalin and stained with toluidine blue and erythrosin, hematoxylin and erythrosin, or cresyl violet. The rest has been prepared by various modifications of the Cajal silver technic.

Histological Data

Relative Frequency of Ganglion Cell Types: As observed in silver preparations, nearly all the ganglion cells in the autonomic ganglia of children and young adults possess only long dendrites. According to de Castro,[2] all the autonomic ganglion cells conform to this type during fetal and early postfetal life. In our preparations of ganglia of young adults, ganglion cells characterized by short intracapsular and glomerular dendrites occur only rarely except in the cephalic parasympathetic ganglia, in which short dendrites are common. Those with both short and long dendrites are more abundant. Since ganglion cells of the latter type are more abundant in the ganglia of adults than in children, it must be assumed that short intracapsular dendrites may arise late in the process of differentiation. This opinion has been expressed by de Castro [2] who designated the short intracapsular processes "secondary dendrites." Preparations of ganglia in the more advanced age groups show both ganglion cells with short and glomerular dendrites and those with both long and short dendrites in greater abundance than in preparations of ganglia of young adults.

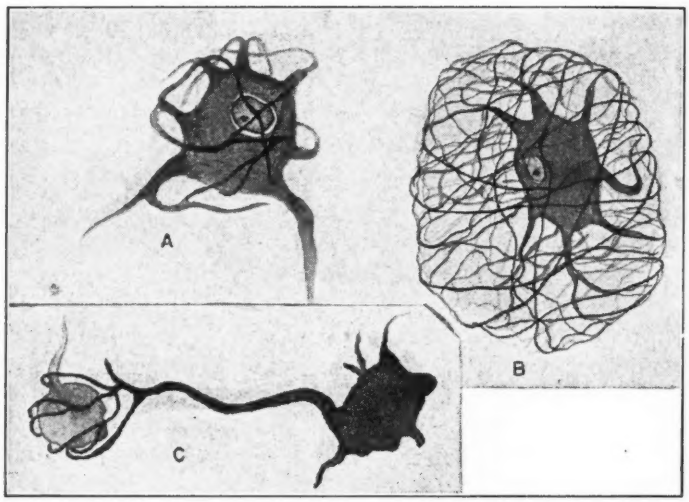
The progressive changes in the dendrites of the ganglion cells are less marked in the cephalic autonomic ganglia than in other

parts of the autonomic system, since short dendrites are relatively abundant in these ganglia in the younger age groups as well as in the more advanced. Intracapsular dendrites are not uncommon in the cephalic autonomic ganglia in all age groups. Many of them are very short and terminate in knob-like enlargements; others are much longer but do not penetrate the ganglion cell capsule. The extracapsular dendrites also are relatively short. Slavich [3] has emphasized the preponderance of ganglion cells with short dendrites in the cephalic autonomic ganglia.

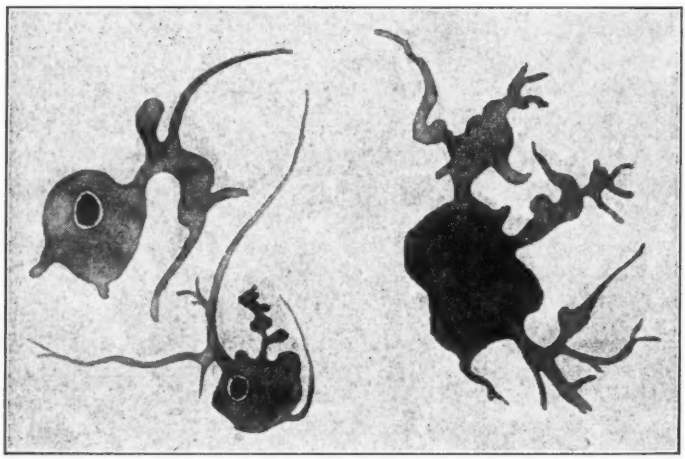
Dendritic Modifications: Silver preparations of ganglia in the more advanced age groups show various modifications of the dendrites of some of the ganglion cells. Intracapsular dendrites and arborizations of extracapsular dendrites are more abundant in many of the ganglia in the advanced age groups than in any of the younger ganglia. New dendrites obviously arise relatively late in life. Some investigators, particularly de Castro [4, 5] and Levi,[6] have supported the assumption that autonomic ganglion cells may undergo continuous growth and differentiation throughout life.

In some of the ganglia in the more advanced age groups (40 years or over) elaborate pericellular dendritic nests are not uncommon. These are formed by dendrites which are wrapped around the ganglion cell bodies from which they arise or the cell bodies of other ganglion cells in the vicinity (Text-Fig. 1). These structures, which de Castro has designated "false articulation nests," probably owe their origin to the enormous elongation of the dendrites involved. In the most elaborate ones the dendritic branches superficially resemble the terminal branches of axons (Text-Fig. 1B and Fig. 4). In the simpler pericellular nests formed on the cell bodies of ganglion cells by the terminal branches of dendrites of adjacent ganglion cells the processes involved retain their typical dendritic appearance (Text-Fig. 1C).

Budding and hypertrophy of the dendrites occur frequently in some of the ganglia in the advanced age groups. Short dendrites not infrequently present a tuberose or beaded appearance and terminate in club shaped enlargements. Longer dendrites sometimes present irregular local thickenings by virtue of which they appear highly distorted (Text-Fig. 2). In some instances dendrites give rise to new processes of variable length and caliber which form more or less complex brushes and tracts (Figs. 1, 2, 3).



TEXT-FIG. 1. Simple (A) and complex (B) pericellular nests formed by dendrites of same cells, and simple pericellular nest (C) formed by dendrite of adjacent ganglion cell, in celiac ganglion, age 44 years.



TEXT-FIG. 2. Celiac ganglion cells with thickened and distorted dendrites, age 78 years.

Structures of this kind have been reported by de Castro, particularly in cases of tabes, alcoholism and multiple sclerosis. Dendritic glomeruli involving two or more ganglion cells also are not uncommon in most of the autonomic ganglia.

Chromidial Substance: The chromidial substance in the ganglion cells may be studied satisfactorily either in the toluidine blue-erythrosin or the hematoxylin-erythrosin preparations. In most of the ganglia of children and young adults in our series the chromidial substance is distributed more or less uniformly throughout the cytoplasm in the majority of the ganglion cells (Fig. 5A and B). Some cells contain a more abundant supply of chromidial substance than others; consequently they react more strongly to the basic stain. In those with only a meager supply of chromidial substance this material usually is distributed in the peripheral zone of the cytoplasm (Fig. 5C), leaving the perinuclear zone relatively devoid of chromidial bodies. Less frequently the chromidial substance is aggregated in the perinuclear zone (Fig. 5D). These observed variations in the quantity and distribution of the chromidial substance in the ganglion cells probably are associated with different phases in the functional activity of these cells.

In some of the ganglia obtained at autopsy, particularly in the advanced age groups and nearly all of those in the surgical series, the supply of the chromidial substance is relatively meager in the great majority of the ganglion cells. The chromidial substance present in these cells in most instances exists in minute granules or as chromidial dust (Fig. 5E). Most of the ganglion cells which contain but little chromidial substance also exhibit some diminution in the size of the nucleus and in the quantity of intranuclear chromatin. Some of these ganglia also include hyperchromatic ganglion cells. The latter usually exhibit shrinkage both of the nucleus and of the cytoplasm (Fig. 5F).

Pigmentation: Melanotic pigment in the cytoplasm of some of the ganglion cells is a common phenomenon in all the ganglia of individuals 30 years of age or over in our series. Ganglion cells containing some melanotic pigment also occur in some of the ganglia in the younger age groups. The youngest in our series which show ganglion cells with appreciable amounts of melanotic pigment are sympathetic trunk ganglia of a patient 11 years of age with progressive muscular dystrophy. Traces of melanotic

pigment in ganglion cells have been reported in younger material. Some of the ganglia in our series which fall within the age limits of 18 to 25 years show moderate pigmentation of some cells, but none below the age of 35 years show marked pigmentation. Some of the ganglia in the most advanced age groups also show only moderate pigmentation.

The quantity of melanotic pigment in pigmented ganglion cells varies within wide limits. In moderately pigmented cells the pigment granules may be distributed in a narrow peripheral zone or aggregated in a restricted portion of the cell body, usually adjacent to the base of one of the larger dendrites. In occasional cells the pigment appears aggregated in a cap shaped mass at one side of the nucleus. As the pigment increases in amount it replaces more and more of the cytoplasm until the entire cell body outside the nucleus appears filled with this material. In some ganglion cells masses of pigment granules occur also in the dendritic processes. In cases of excessive pigmentation masses of pigment outside the ganglion cells are not uncommon, although some of the ganglion cells remain devoid of pigment (Fig. 6).

Many moderately pigmented ganglion cells exhibit no other histological changes except some reduction in the quantity of chromidial substance. Excessive pigmentation probably always is accompanied by other degenerative changes in the ganglion cells and results in the death of many of these cells. As the normal cytoplasmic constituents are replaced by pigment granules the ganglion cells undoubtedly become functionless. In silver preparations of heavily pigmented ganglia the dendrites and axons of many of the ganglion cells that are most heavily laden with pigment are not impregnated, although the processes of adjacent ganglion cells which are devoid of pigment or only moderately pigmented are impregnated perfectly (Fig. 6). Excessive pigmentation undoubtedly results in necrosis of a large percentage of the ganglion cells. In the most heavily pigmented ganglia in our series the majority of the ganglion cells obviously are necrotic. Even in these ganglia many of the ganglion cells are devoid of pigment. In moderately pigmented ganglia only the most heavily pigmented cells appear to be necrotic.

The most heavily pigmented ganglia in our series are those that have been obtained following death from carcinoma. They fall

within an age range of 46 to 77 years. In general the younger ones are less heavily pigmented than the older but the difference is not very marked except in the most extreme cases. The youngest ganglia in this group are much more heavily pigmented than most of the other ganglia in the same age group and some of those in the most advanced age group. The excessive pigmentation of the autonomic ganglion cells in this group of patients undoubtedly is associated with the malignant disease. Excessive pigmentation of the autonomic ganglion cells probably is a constant accompaniment of carcinoma, particularly in its advanced stages.

Other Cytological Variations: In the ganglia of children and young adults in our series, except those obtained from surgical cases, the ganglion cells appear highly uniform in their internal structure and present no variations that could be regarded as pathological. Preparations of some of the ganglia obtained at autopsy beyond the ages of young adults and those of nearly all the ganglia in the surgical series show changes other than pigmentation and variations in the chromidial substance, in some of the ganglion cells, which obviously represent degenerative processes. These changes include hyalinization of the cytoplasm in ganglion cells with a meager supply of chromidial substance, hydropic enlargement or edema of a small number of ganglion cells, vacuolization of the cytoplasm in some, neurofibrillar changes in some, and destruction of cytoplasm by phagocytic cells in variable numbers (Fig. 7).

Interstitial Tissue: In toluidine blue-erythrosin and hematoxylin-erythrosin preparations of ganglia of young children the connective tissue framework appears relatively meager. The ganglion cell capsules are inconspicuous and the ganglion cells are closely aggregated in groups which are separated from one another by bundles of axons and long dendrites. Cells probably homologous with neuroglia are present among the dendrites as well as in association with the axons. In preparations of the ganglia of young adults the interstitial connective tissue is somewhat more abundant. The ganglion cell capsules are less delicate than in the younger material, but the ganglion cells within groups remain closely aggregated. The groups are separated somewhat more widely by the increasing volume of the dendrites and axons.

Preparations of the ganglia in the more advanced age groups

which exhibit the narrowest ranges of variation in the ganglion cells show a moderate progressive increase in the amount of connective tissue in the framework of the ganglia and slight thickening of many of the ganglion cell capsules. The interstitial tissue, plus the ganglion cell processes, makes up an appreciably greater percentage of the volume of the older than of the younger ganglia.

Some of the ganglia in our series in all the age groups show relatively wide variations in the interstitial tissue. Some of these variations undoubtedly are associated with acute or chronic infections or other inflammatory processes.

Preparations of all the ganglia obtained following death from acute infectious disease show evidence of marked hyperemia of the interstitial tissue and infiltration with wandering cells, including mainly lymphocytes and mononuclear leukocytes. These cells appear in greatest abundance in the perivascular lymphatics, but also occur throughout the interstitial tissue and, in many instances, within the ganglion cell capsules. In some of the ganglia the interstitial connective tissue shows evidence of hyperplasia.

Preparations of ganglia of individuals with chronic infectious disease usually show less hyperemia of the interstitial tissue than those of ganglia obtained from cases of acute infectious disease. Infiltrating cells also are less abundant, but hyperplasia of the interstitial connective tissue is more marked and proliferation of the cells lining the ganglion cell capsules is not uncommon. Hyperplasia of cells other than those of connective tissue origin also takes place, which accounts for a large percentage of the cellular elements present throughout the interstitial tissue. These factors probably are associated with the inflammatory process.

The above account of the changes observed in the interstitial tissue in autonomic ganglia in acute and chronic infectious disease is in general agreement with those of Staemmler [7] and Mogilnizcky.[8, 9, 10] These investigators regarded the hyperemia, infiltration and hyperplasia of the interstitial tissue, with accompanying changes in ganglion cells, in the autonomic ganglia in infectious disease as related to the disease process, but not as direct factors in the etiology of the disease.

Preparations of most of the ganglia removed surgically in our series show changes in the interstitial tissue comparable with those observed in the ganglia in instances of chronic infectious

disease. Inasmuch as changes such as these afford evidence of chronic inflammation in the ganglion, they may be regarded as accompaniments of the diseases in question.

Comment

The histological data set forth above show that preparations of autonomic ganglia falling within any given age group exhibit certain variations common to all the ganglia in that group, but the ganglia of certain individuals in every age group exhibit a wider range of variation than those of others. This is due in part to the presence of certain variations in some cases which are not common to all in the same age group and in part to the existence in exaggerated form of certain of the common variations. The ganglia in every age group which exhibit only those variations that are common to all ganglia within that group undoubtedly may be regarded as most nearly normal. The variations they exhibit, consequently, are related to age. Variations that exist in some of the ganglia in a given age group and not in others obviously depend on factors other than age. Some of these variations undoubtedly are pathological in some degree. The existence in exaggerated form of certain variations common to all ganglia in the same age group probably is causally related to pathological lesions in the body which either affect the entire organism or at least result in modifications of metabolic functions.

Changes in the autonomic ganglia indicated by the variations in the successive age groups which, according to the criteria suggested above, may be regarded as related to age include the following: growth and differentiation of the ganglion cells from birth to maturity; development of secondary dendrites and other dendritic modifications in some of the ganglion cells during adult life; deposition of melanotic pigment in moderate amounts in some of the ganglion cells, particularly after the age of 30 to 35 years; exhaustion of the chromidial substance in some ganglion cells; degenerative changes in occasional ganglion cells particularly in advanced age, including hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia in moderate degree, and necrosis; moderate progressive increase in the quantity of interstitial connective tissue from birth to advanced age; and thickening of the ganglion cell capsules in some

degree and the occasional existence of free cells within the ganglion cell capsules, particularly in advanced age. Changes which, according to the same criteria, may be regarded as pathological include the following: elaborate development of dendritic nests, dendritic brushes, and so on, and excessive budding and hypertrophy of dendrites; marked chromidial changes in large numbers of ganglion cells, including diminution of the supply of this substance in some cells and hyperchromatism in others; excessive deposition of melanotic pigment in the ganglion cells; marked degenerative changes in considerable numbers of ganglion cells, particularly in the less advanced age groups, including hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia and necrosis; hyperemia and infiltration of the interstitial tissues and hyperplasia of both connective tissue and non-connective tissue elements; and marked thickening of ganglion cell capsules with proliferation of the cells lining them.

Histological variations in autonomic ganglia which obviously are related to the age of the individual probably depend on progressive changes in the metabolic processes in the organism. Those that are related to disease undoubtedly depend on factors associated with the disease processes in question. The common occurrence of hyperemia and infiltration of the interstitial tissue in the ganglia in acute or chronic infectious disease, and other conditions in which lesions of ganglion cells are common, strongly suggests that acute or chronic inflammation in the ganglia bears a causal relation to the ganglion cell lesions in many cases. The ganglion cell lesions in such cases, consequently, must be regarded not as causes but as accompaniments of the disease in question. Certain ganglion cell lesions, *e.g.*, excessive pigmentation, probably result from functional depression of the ganglion cells (Dolley and Guthrie [11]). Since excessive pigmentation is a constant accompaniment of certain pathological states, *e.g.*, arsenic poisoning, cachexia and senile atrophy, it probably must be regarded as a direct result of the pathological state in these cases.

All the observed histological variations in autonomic ganglia that have been regarded as related to disease fall into relatively few general categories. Those associated with diverse diseases, furthermore, may be essentially similar; consequently they cannot be regarded as specifically related to the disease in ques-

tion in any given case. This point of view has been supported by nearly all investigators who have studied the histological variations in autonomic ganglia in relation to disease. As the author [12] has previously pointed out, however, most of the variations observed in autonomic ganglia which obviously are related to disease are indicative of hyperactivity of the ganglion cells. Therefore, it seems not improbable that the autonomic dysfunction associated with these changes may have played a rôle in the disease process in question, particularly in cases in which vasoconstriction was a factor in the disease. The autonomic dysfunction resulting from necrosis or physiological depression of a large percentage of the ganglion cells in certain cases probably also plays a rôle in the disease process in these cases.

Summary

Histological variations in autonomic ganglia and ganglion cells have been studied in preparations of ganglia obtained at autopsy in an extensive series of unselected cases and ganglia removed in the surgical treatment of disease in approximately 50 cases. These ganglia represent an age range from early childhood to senility. The ganglia in every age group that exhibit only variations common to all the ganglia within that group have been regarded as most nearly normal. The variations observed in them, consequently, have been regarded as related to age. Variations not common to all the ganglia within a given age group and certain variations common to all the ganglia in the same age group but existing in exaggerated form have been regarded as pathological in some degree and causally associated with pathological lesions in the body.

The variations that have been regarded as related to age include all changes resulting from normal growth and differentiation both in the ganglion cells and in the interstitial tissue, changes in the chromidial content of ganglion cells associated with normal functional activity, deposition of melanotic pigment in moderate amounts in some ganglion cells, and degenerative changes in occasional cells, particularly in advanced age. Those that have been regarded as related to disease or pathological lesions in the body include the following: marked chromidial changes in large numbers of ganglion cells; excessive deposition of melanotic pigment

in ganglion cells; marked degenerative changes in considerable numbers of ganglion cells, such as hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia and necrosis; hyperemia and infiltration of the interstitial tissue and hyperplasia of both connective tissue and non-connective tissue elements; and marked thickening of ganglion cell capsules and proliferation of the cells lining them.

The observed variations in the ganglia that seem to be related to disease fall into a few general categories. Those associated with diverse diseases, furthermore, may be essentially similar; consequently, they cannot be regarded as specifically related to the disease in question in any given case.

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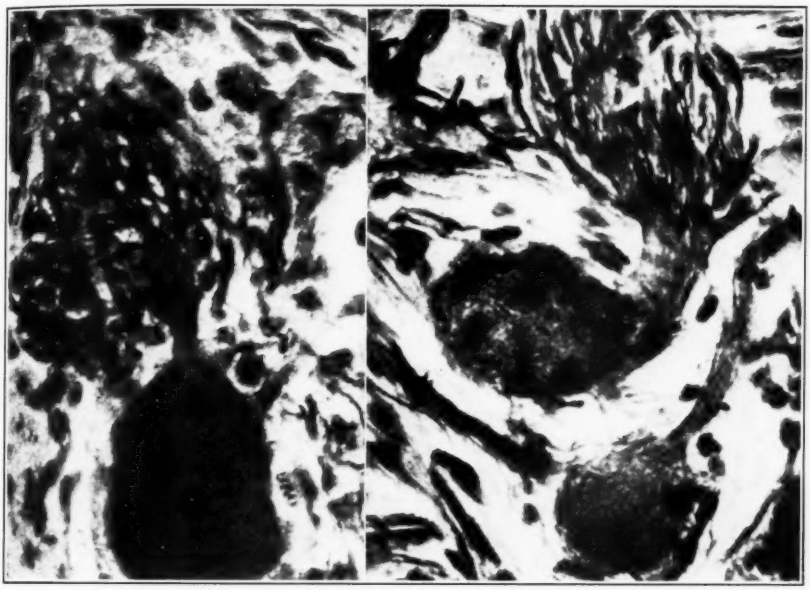
DESCRIPTION OF PLATES

PLATE 147

FIGS. 1, 2, 3 and 4. Ganglion cells showing pathological dendritic modifications from a patient aged 78 years.



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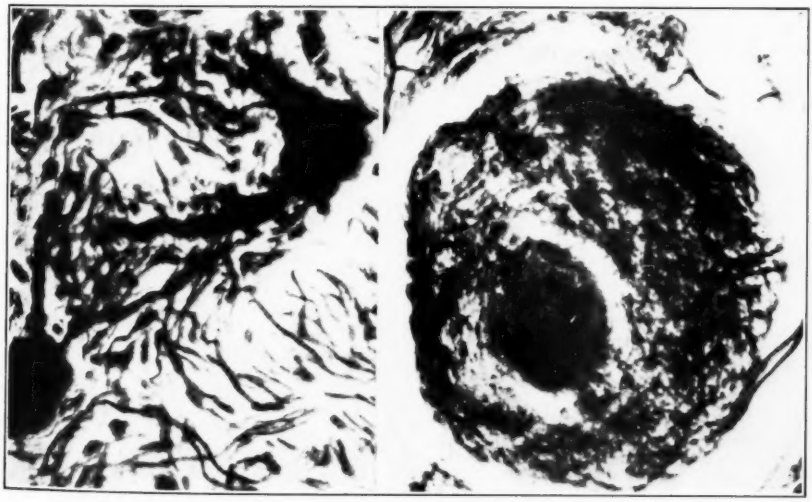


3 4

Kuntz

Autonomic Ganglia and Ganglion Cells

PLATE 148

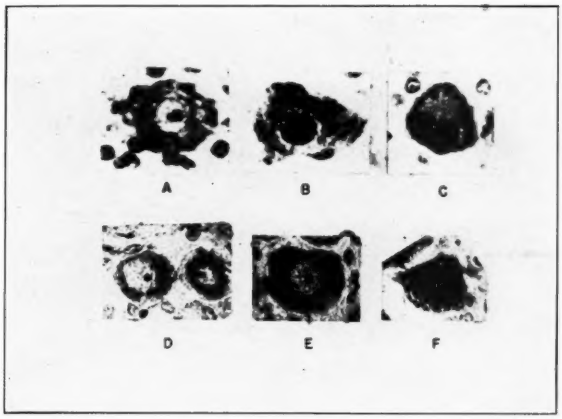
FIG. 5. Autonomic ganglion cells illustrating variations in distribution and quantity of chromidial substance.

A = uniform distribution, chromidial bodies large; B = uniform distribution, chromidial bodies small; C = peripheral distribution; D = perinuclear distribution; E = chromidial dust; F = hyperchromatic cell.

FIG. 6. Heavy pigmentation in sympathetic trunk, patient with carcinoma, age 77 years.

FIG. 7. Ganglion cells.

A = hyaline degeneration; B = hydropic enlargement; C = vacuolization; D = neuronophagia.



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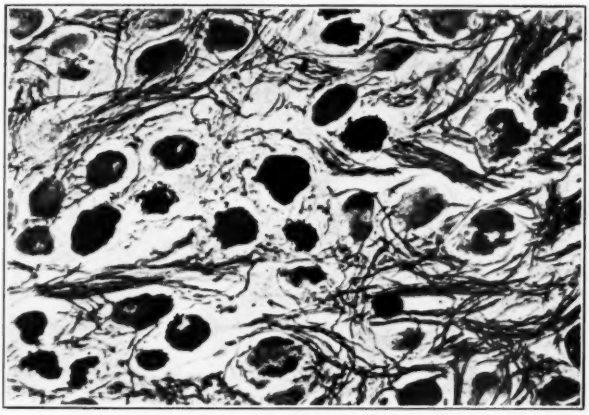

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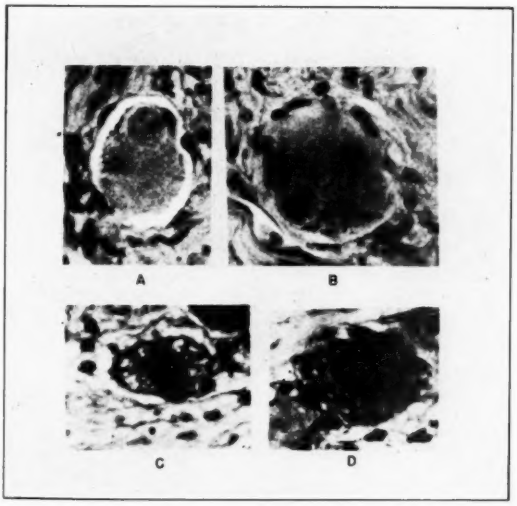

7

MULTIPLE TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM *

Report of a Case Showing a Distinct Ganglioneuroma, a Neuroblastoma and a Cystic Calcifying Ganglioneuroblastoma

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The sympathetic nervous system is the site of an uncommon but interesting group of tumors — the ganglioneuroma, the neuroblastoma and the paraganglioma. While a few of these tumors are reported as arising from the central nervous system, the great majority arise from the embryonic formative nerve cells of the sympathetic nervous system whose differentiation determines the structure and behavior of the tumor. The malignant type is composed of undifferentiated neurocytes and is usually referred to as the sympathetic neuroblastoma. The benign types may be made up either of ganglion cells and nerve fibers forming the ganglioneuroma or of chromaffin cells producing a paraganglioma. Various transitions between these different forms have been reported [32, 33, 12] and two or even three types may be included in one tumor.[16, 54, 23] Moreover, a multicentric origin of these tumors in various parts of the sympathetic nervous system has been noted.[30, 28] Thus far they are usually of the same type, but undoubtedly they may include all three types occurring independently of each other. Such multicentric tumors would imply a widespread neoplastic change in the sympathetic nervous system.

Usually a single primary ganglioneuroma is described and several excellent reviews of these cases are available [33, 32, 12] so that a discussion of the literature on these types would be superfluous. However, the occurrence of multiple primary tumors arising from the sympathetic nervous system is not so generally recognized.[33] All three types, but especially the ganglioneuromas and paragangliomas, have been reported as multicentric in origin.

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Eight cases of undoubted multiple ganglioneuromas were noted in the literature. The first case, described by Knobellauch in 1843 and quoted by McFarland and Sappington,[33] showed a tumor of nerve cells and fibers in the facial region and another of the same type in the sacral area. Busse [10] described a patient with a ganglioneuromatous mass in the pelvis and another under the ribs. Knauss,[28] Kredel and Beneke,[30] and Montgomery and O'Leary [40] described multiple cutaneous and subcutaneous nodules containing ganglion cells and nerve fibers somewhat resembling the neurofibromas of the central nervous system in von Recklinghausen's disease but having their origin in the sympathetic nerve twigs about the cutaneous vessels. Roman and Arnold [48] describe a peculiar diffuse ganglioneuromatosis due to a widespread embryological disturbance of the sympathetic trunk producing an extensive retroperitoneal growth. Haven and Weil [21] reported multiple growths in the cervical region with another in the pelvis. Bigler and Hoyne [6] noted such a tumor in the mediastinum and another under the right clavicle. There is some question as to whether the so-called malignant ganglioneuroma [38] is not in reality a multiple tumor belonging to this group.[52]

The paraganglioma is frequently reported as being bilateral.[4] Marchetti [34] was the first to describe bilateral adrenal tumors and Belt [4] has noted 7 additional cases. Popken [42] and Kremer [31] each describe bilateral paragangliomas of the adrenals. Rosenthal and Willis [49] note such a bilateral involvement associated with multiple neurofibromas. The work of Huebschmann [24] and Masson,[35] supported by the reports on carcinoids by Cooke,[11] Raiford,[43] Reid,[44] Forbus,[18] and Lewis and Geschickter,[32] would indicate the identity of the paraganglioma and the carcinoid (argentaffin) tumors of the intestinal tract. This theory is based on the similarity in the structure and the affinity for chrome salts and silver salts of both these groups of tumors. Accordingly, multiple primary carcinomas of the intestines, such as described by Bunting,[9] represent multiple malignant paragangliomas of the sympathetic system. These carcinoids tend to be single and benign when they arise in the appendix,[53] but multiple and malignant when occurring in the intestines. If subsequent studies confirm the identity of the carcinoid and the paraganglioma, the most frequent multiple tumor of the sympathetic system would be the carcinoid of the intestinal

tract. For instance, Cooke analyzes 104 cases with 8 multiple tumors in the malignant forms and 21 multiple tumors in the benign group.

The neuroblastoma may also be multiple [15] although this has been more difficult to demonstrate because of the ever present possibility of early metastases, such as illustrated in Berner's case.[5] The combination of a benign type with an independent malignant form arising from the sympathetic trunk probably may occur but no such case has been found in studying the literature. Such an unique case comprising an independent benign and a malignant growth, and a third independent growth intermediate in structure forms the basis of this report.

Report of Case

Clinical History: The patient was a negro, aged 28 years. He had had "rheumatism" for over a year and had become bedfast. He complained of headache and tender spots on the skull. Following a chiropractic adjustment he developed paralysis from the waist downward, associated with urinary retention and fecal incontinence. X-ray examination of the lower spine and pelvic bones showed "extensive destruction of the entire right ilium with the exception of the crest. This destruction consists of a mottled, moth-eaten appearance characteristic of metastatic malignancy." There was also involvement of the acetabulum and superior ramus of the pubic bones on the right. A similar infiltration was seen in the sacrum and left ilium and lower lumbar vertebrae with collapse of the second and fourth lumbar vertebrae. The X-ray also showed a partly calcified tumor mass high in the pelvis on the left. A few days prior to death symptoms of intestinal obstruction supervened and it was regarded as the immediate cause of death.

Postmortem Examination

The autopsy showed an intestinal intussusception in the lower ileum. When this was opened two pedunculated polypoid masses were present in the thickened and edematous mucosa. Three independent tumor masses were found in the retroperitoneal region of the pelvis. One was a small oval tumor mass (Figs. 1 and 2b) weighing 48 gm., situated in the right iliac fossa adherent to the right iliac artery and vein and associated with the fascia of the psoas muscle. This mass measured 6 by 5 by 2 cm. It was soft and well outlined and cut easily. The freshly cut surface was granular and friable in appearance and of a dark reddish purple color. At the upper part of this mass there were a few fused

enlarged lymph nodes, some of which showed on cut section considerable blood pigment and granular, friable cellular foci indicating tumor metastases.

The second pelvic mass (Figs. 1 and 2a) was attached to the sigmoid colon and to the lower right brim of the pelvis, weighed 60 gm. and measured 6 by 5 by 4 cm. It was rounded in shape and well outlined. It was firm and rubbery in consistence, cut with some resistance, and the cut surface had a wet, glistening white appearance. Nerves could be traced into and were lost in this mass. In some areas the cut surface showed a loose, moist edematous stroma, while in other places it had a wet, glistening, white homogeneous appearance.

The third mass (Figs. 1 and 2c) was also rounded in shape, weighed 98 gm., and measured 7 by 7 by 5 cm. Its surface was roughened and nodular. It was entirely independent of the other two masses and was buried below the second mass deep in the iliac fossa, being adherent to the endopelvic fascia and to the inner wing of the left ilium (Fig. 2c). There were a few loose blood clots on the outer surface. The mass was mainly cystic in character, enclosing blood clots and hemorrhagic jelly-like material. Its wall was largely calcified and measured 3 to 5 mm. in thickness. Its inner surface was ragged and hemorrhagic. Scattered gray cellular masses were embedded in the wall enclosed by heavy white fibrous tissue. Some of these cellular foci were 1 to 2 cm. in diameter, were soft and friable, and in one field presented a gritty consistence as if composed of sand in soft tissue, suggesting many small calcareous deposits. Nerve fibers could be traced into the wall of this hemorrhagic cyst. A few portions of this cystic wall had a moist, wet, homogeneous white appearance such as occurred in the second mass.

No metastases could be detected in the liver or in any other viscera except in a few large lymph nodes adjacent to the first mass. The bodies of the lumbar vertebrae were softened and crushed, and could be cut easily with the knife. The cut surface had the same reddish gray friable appearance as the cut section of the metastases in the lymph nodes in the first mass. Similar softened grayish tissue extended into the sacrum and the adjacent ileum. No other tumor tissue could be found.

Histological Examination

Microscopic examination of the polypoid masses in the small intestine at the site of intussusception showed a diffuse acute inflammatory reaction, in fact in many places a phlegmonous appearance was present not only in the polyp but also in the adjacent intestinal submucosa.

The sections through the mass in the right iliac fossa showed a loose cellular tumor tissue in which there were numerous small cells with scanty cytoplasm and rounded nuclei rich in chromatin embedded in a delicate fibrillar reticulum which often had an intimate relation to the cytoplasm of the cells, many of which were arranged in balls, clumps and clusters with a central mesh of fibrils forming "rosettes" (Figs. 3, 4, 5). The outlines of the tumor cells were often obscure, the cytoplasm scanty and often present at one side of the cell with a tendency to extend into a protoplasmic process that blended with the fibrillated stroma (Fig. 3).

The large lymph nodes adherent to this mass were largely replaced by masses of these tumor cells. Most of the lymphoid tissue not involved by the tumor tissue contained considerable yellowish brown pigment enclosed in masses of large mononuclear phagocytes. This pigment gave a positive Perles' test and was most probably blood pigment. Blocks of the softened vertebrae were cut and lost, but since the gross material was the same as that of the mass in the right iliac fossa and adjacent lymph nodes, it was considered probable that this was the same type of tissue. This cellular tissue showed numerous hemorrhages but there was no intimate relation between the tumor cells and the vessels.

The histological study of the second tumor mass, attached to the sigmoid colon, presented a very different picture. It was composed mostly of loose edematous fibrillar tissue at one side of which was much denser fibrous tissue. In this denser area were larger and smaller nests of ganglion cells (Fig. 11) and interlacing nerve fibers mostly of the non-medullated type. Secondary edema and even cystic degeneration were encountered, especially in the nests of ganglion cells (Fig. 9). Occasionally a few clumps of monocytes somewhat resembling the undifferentiated tumor cells were found on careful search. Some of these were found in the nest of ganglion cells. No evidence of regeneration could be seen

in this tissue, in fact the ganglion cells tended to be degenerated. Silver stains showed typical axis cylinders passing out of the ganglion cells and becoming lost in the surrounding mesh of fibrils. Delicate neurofibrils often suggesting a basket-like mesh could be recognized about some of the ganglion cells. Some of the ganglion cells which tended to be oval or elongated in shape contained a large nucleus with an unusually large distinct nucleolus.

The microscopic appearance of the third cystic mass was quite variable in different fields. In a large part of the tumor the wall of the cyst was composed of dense collagenous fibrous tissue showing considerable tendency to calcification and in some places even osseous metaplasia with pseudo bone marrow formation. In other fields the wall was more fibrillar and scattered ganglion cells could be recognized (Fig. 8). In still other nodular areas of softened tissue, embedded in the cystic wall, hemorrhagic cellular foci occurred with the same clumping of the small cells with rosette formation noted in the first mass described, indicating the presence of neurocytes embedded in a fibrillar syncytial reticulum (Figs. 6 and 7). In other fields the cells were more differentiated and the fibrils were arranged in parallel bundles with tumor cells at each end, giving the appearance of sheaves of wheat. In these areas a few, large, more mature cells were seen suggesting immature ganglion cells (Fig. 8). In fact all transitions from neurocytes and ganglion cells could be identified. In some fields this cellular tissue showed extensive deposits of calcium salts in the fibrils (Fig. 6), thus accounting for the gritty sensation noted in gross.

Anatomical Diagnoses: Ganglioneuroma of sigmoid colon and pelvis; neuroblastoma of pelvis with metastases to regional lymph nodes and widespread skeletal metastases; blood pigmentation of lymph nodes; ganglioneuroblastoma of pelvis with extensive secondary hemorrhage, cystic degeneration, calcification and osseous metaplasia; and acute polypoid phlegmonous enteritis with intussusception and intestinal obstruction.

Discussion

The three tumor masses just described bear no direct anatomical relation to each other. They are derived independently from the lower end of the sympathetic trunk and represent different degrees

of differentiation of the same primitive formative neurocyte with the malignant neuroblastoma with lymph node and skeletal metastases on the one hand and a benign ganglioneuroma on the other. While there may be some question as to the independence of the calcified cystic mass and the more cellular (neuroblastoma) mass on the right, there can be no doubt of the independence of the ganglioneuroma. The evidence that the other two are also independent is based on the failure to find any connection between them grossly and the difference in their microscopic structure. One is a rapidly growing cellular growth with invasion into adjacent lymph nodes and bone, while the other shows extensive hemorrhage, calcification, ossification and all stages in differentiation to adult nerve tissue. This lesion seems to be a stage intermediate between the malignant neuroblastoma and the benign ganglioneuroma, that is, a so-called ganglioneuroblastoma.

These three tumor masses comprise a remarkable instance of three independent primary tumors arising from the lower end of the sympathetic system, each different in structure and appearance and representing three stages in the differentiation of the malignant neuroblastoma to the ganglioneuroblastoma and to the ganglioneuroma. The cystic and hemorrhagic mass with a partly calcified wall contained structures resembling the embryonic neurocytes and also had more differentiated nerve cells and fibers in addition to unusual degenerative changes, especially hemorrhage, cystic degeneration and calcification. No paraganglionic tissue was found but there is no reason why a tumor containing this type may not occur.

The striking tendency to hemorrhage, cystic degeneration and calcification is worthy of additional comment. Edema and cystic degeneration are frequently noted in ganglioneuromas.[5, 29, 26]

Hemorrhage and cystic degeneration are also commonly noted in malignant neuroblastoma [2, 45] and ganglioneuroblastoma,[16] but calcification in the cystic wall is unique in the literature, especially in association with osseous metaplasia and bone marrow formation, though McFarland [33] and Berner [5] do refer to the occurrence of liquefaction and calcification. Cystic degeneration and hemorrhage are also frequently described [32] in the paraganglioma.[19]

The age at which these tumors occur may be worthy of comment. For many years the malignant neuroblastoma was thought

to be present in young children only and not until 10 years ago were any cases reported in older children, but while they are most common in early life a considerable number of cases in later adult life have been reported. Alyea,[1] for instance, reported a case of a man 55 years of age, and noted two other adults in his series, so that the fact that our case was in an adult is not unusual.

Summary

A case of multiple tumors of the sympathetic nervous system is reported illustrating three types of growth arising from the sympathetic system and representing three stages in differentiation of the formative neurocyte, *viz.* neuroblastoma, ganglioneuroblastoma and ganglioneuroma.

Multiple neurogenous tumors of all types have been reported arising from the sympathetic system. If the theory that the paraganglioma is identical with the carcinoid of the gastro-intestinal tract is true, this is the most common multiple and even single tumor of the sympathetic nervous system.

These tumors often show a tendency to cystic degeneration, hemorrhage and calcification, especially the more malignant types.

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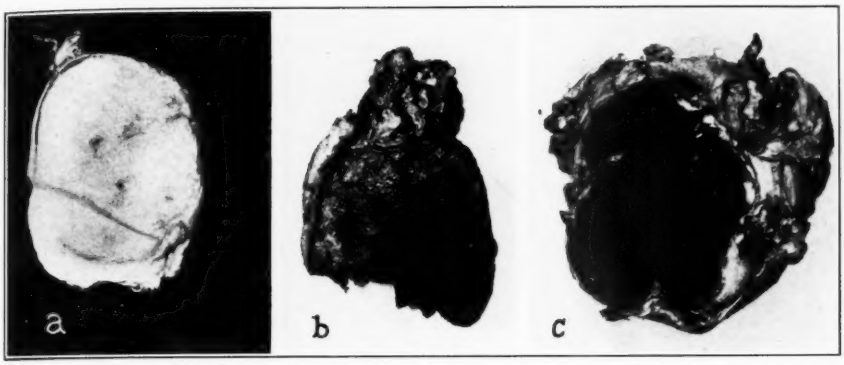
DESCRIPTION OF PLATES

PLATE 149

FIG. 1. Gross photographs of cut sections through each of the tumor masses. 2/3 actual size.

a = ganglioneuroma.
b = neuroblastoma.
c = ganglioneuroblastoma.

FIG. 2. Diagrammatic sketch indicating the location and origin of the tumors. Lettering as above.



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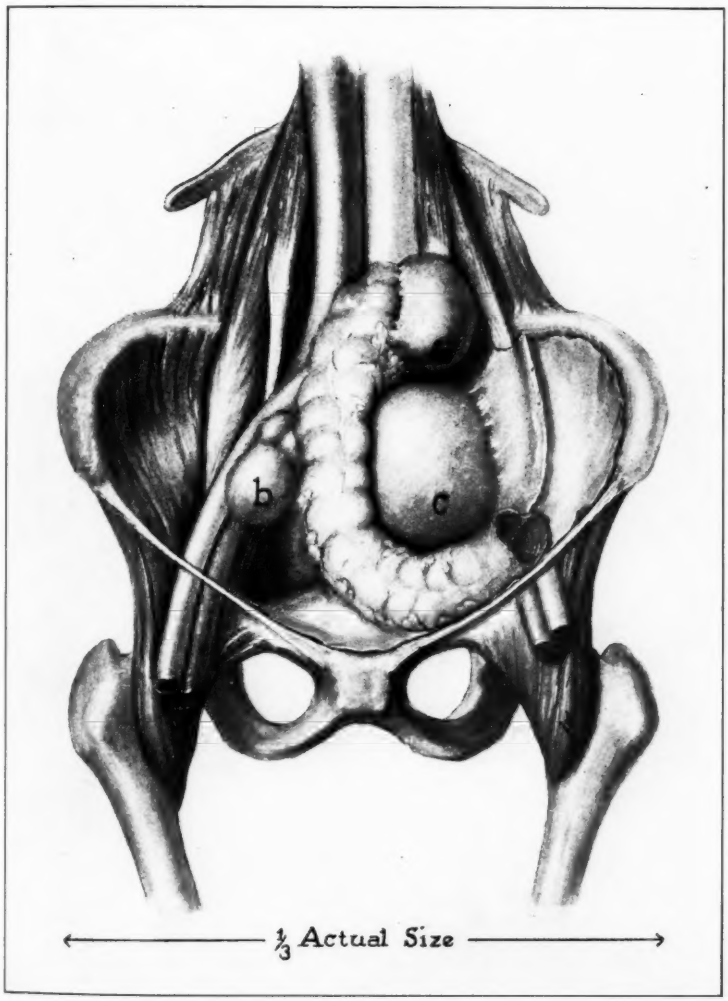


2

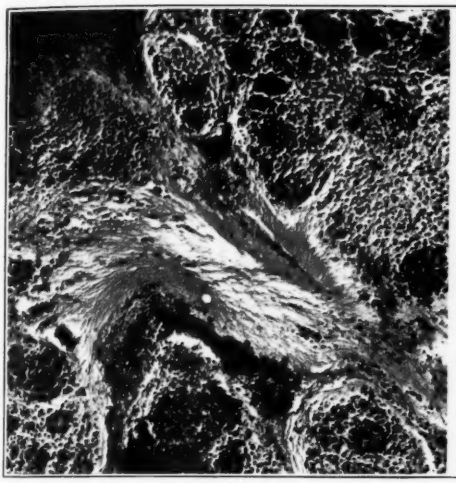
Wahl and Craig Multiple Tumors of Sympathetic Nervous System

PLATE 150

FIGS. 3, 4 and 5. Microphotographs of the neuroblastoma (Figs. 1 and 2b) showing rosettes, neurocytes and fibrillar matrix. Hematoxylin and eosin stain. × 100.

FIGS. 6 and 7. Microphotographs of the ganglioneuroblastoma (Figs. 1 and 2c) showing rosettes, fibrillar matrix, hemorrhages (x) and calcification (y). Hematoxylin and eosin stain. × 100.

FIG. 8. Microphotograph of the ganglioneuroblastoma stained by Bielschowsky's method showing immature ganglion cells as well as neurocytes, and at the lower edge masses of neurofibrils. × 100.



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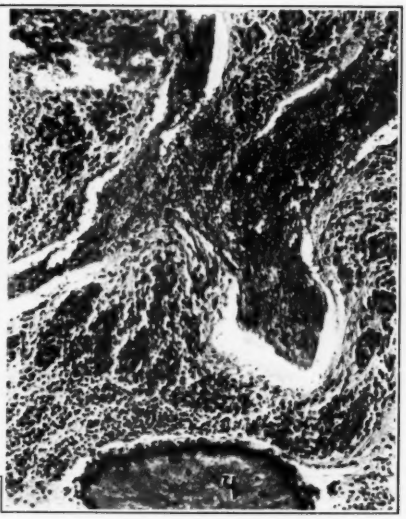

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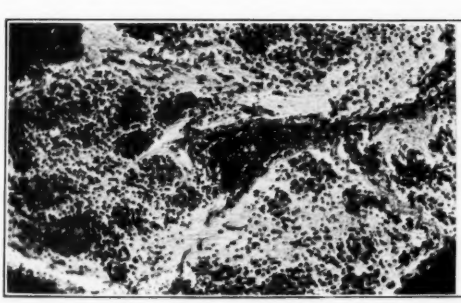

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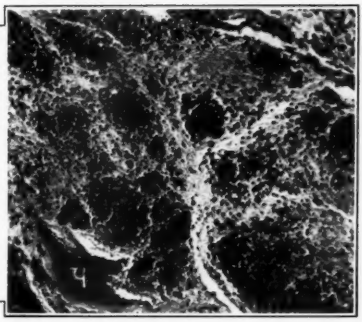

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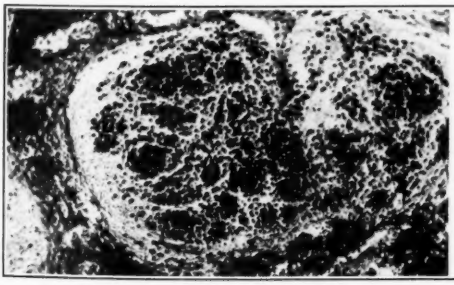

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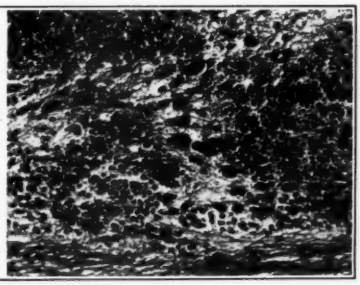

8

Wahl and Craig

Multiple Tumors of Sympathetic Nervous System

PLATE 151

FIG. 9. Microphotograph of a Bielschowsky's silver impregnation preparation of the ganglioneuroma showing clumps of ganglion cells embedded in a neurofibrillar matrix. Note the edema and cystic degeneration, especially at "x." × 100.

FIG. 10. Microphotograph of a Bielschowsky's silver impregnation method preparation of the ganglioneuroma toned with gold chloride. Ganglion cells and neurofibrils are evident. × 100.

FIG. 11. Microphotograph of a hematoxylin and eosin preparation of the ganglioneuroma. Ganglion cells are embedded in dense bundles of neurofibrils. × 100.

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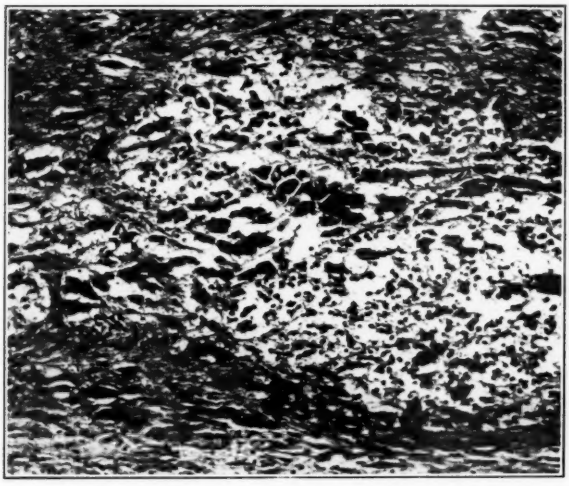

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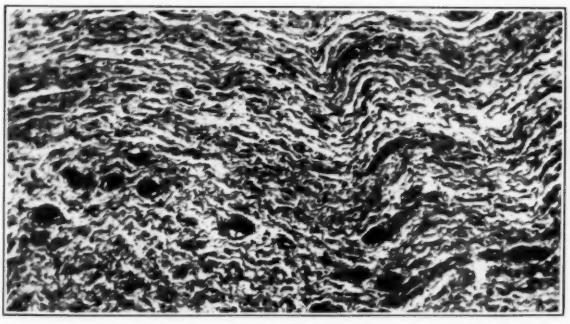

11

Wahl and Craig Multiple Tumors of Sympathetic Nervous System

THE AMOUNT OF SPLENIC LYMPHATIC TISSUE AT DIFFERENT AGES *

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In connection with a study of the postmortem weight of the human spleen at different ages (Krumbhaar and Lippincott [1]), it was desired to know also the amount of lymphatic tissue in the human spleen at these ages. This question has interested investigators ever since Kölliker [2] in 1849 established the fact that the malpighian follicles were composed of lymphatic tissue. Among early estimates are von Hessling's [3] (1842) that the lymphatic tissue occupied about one-fifth to one-sixth the total volume of the spleen; Gray's [4] (1854) of from one-eighth to one-fourth; and Kölliker's that it constituted one-fifth to one-sixth the volume of the red pulp. More recently Groll [5] in 1919 found in healthy young soldiers that the lymphatic tissue of the spleen was best developed in his youngest group (19 and 20 years), and least well developed in those over 41 years of age. The excellent quality of this material, however, is considerably offset by his inability on field service to do more than estimate the size of the follicles macroscopically.

By far the most valuable work in this field is Hellman's [6] (1925–1926, with historical review) analysis of 100 cases, divided into 11 age groups, of persons dying sudden violent deaths and proved at autopsy to have no noteworthy lesions of the spleen. This is truly admirable material, all of the individuals dying within 12 hours of the injury (most of them instantaneously, and all but one within 3 hours), and all studied grossly and microscopically and by the same person. They present a striking curve of quick increase of percentage of lymphocytic tissue in the malpighian follicles from birth to an average of about 11 per cent in the 1st

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† Part I of thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Medical Science (D.Sc.(Med.)) for graduate work in pathology.

year of life, rising to a maximum of 18 per cent in the 18th year, with a sharp drop to 13.6 per cent at 25, remaining level till 45, then another drop to below 5 per cent in the oldest case studied (84 years). One hundred cases, however, is a very small number when distributed over 11 groups, especially as the individual "scatter" was great. There were, for instance, 12 cases below 1 year and 20 below 6, leaving an average of 10 cases for each of the other age groups and only 5 cases over 50 years of age. It should also be noted that the figures given represent percentages only and must be taken in connection with the total spleen weights in order to arrive at the actual amount of lymphoid tissue in the spleen at a given age. Furthermore, they represent only the size of the malpighian follicles, the outer edges of which are often open to considerable interpretation, and they include the intrafollicular vessels and all "pale centers," which many now believe not to be made up of cells of the lymphocytic series. Although the short interval between injury and death precludes changes secondary to wasting, sepsis, and so on, the considerable splenic pulp change that results quickly after shock or hemorrhage cannot be excluded and remains a variable affecting the percentage that cannot be accounted for. We therefore thought that a similar study would be desirable, even though our series is also open to some of the above objections, hoping that larger numbers, especially in the older groups, would throw further light on the subject.

Methods

We have used human material * from 300 cases of violent death, excluding individuals who were found either from the history or the postmortem examination to have any recognizable disease. As Hellman [6] has shown that malpighian follicles are distributed with great uniformity throughout the spleen, and as we were able to confirm this in 1 extensively studied case, we have in each case been content with 1 or 2 sections from the convex surface of the organ and prepared hematoxylin-eosin stained sections of 6 μ thickness. The percentage of lymphatic tissue was obtained by projecting low power ($\times$ 8.6) microscopic fields on 8½ by 11 inch paper, under fixed conditions. The outlines of the malpighian follicles

* Obtained with the kind assistance of Drs. Helpern of New York, Werne of Jamaica, L. I., and Wadsworth and Crane of Philadelphia.

were traced and also their contained non-lymphatic tissue (central artery and pale staining reaction centers noted by Hellman) and both areas measured with a planimeter. The percentage of the area of the follicle as a whole is termed the "gross" percentage (*i.e.*, white pulp), and that of the follicle minus the central artery and pale center, the "net" percentage. When a marginal zone (aussenrandzone) of the follicle, where the lymphocytes are less concentrated, was found, it was not included in the area measured, as better measurement was possible where the much sharper transition occurred at its inner edge than where it gradually merged into the red pulp. In fact, not infrequently the transition to the red pulp was so gradual that a line of demarcation would have been a purely arbitrary one. This of course means that our percentages do not represent the actual amount of lymphatic tissue in the follicles, but this is also true of other studies that have included artery and pale centers in the follicular area. Furthermore, the true lymphocytic content of the spleen as a whole cannot be measured in any case because of the considerable number of lymphocytes both in the Lymphscheiden (lymph sheaths) and scattered through the red pulp. Our method also provides for obtaining a figure for the number of malpighian follicles per unit area. Furthermore, the weight of the spleen being known, an approximate value, limited by the considerations given above, can be obtained for the weight of the lymphatic tissue in the spleen; and, the body weight being known, the ratio of this lymphatic tissue weight to body weight may be determined (Chart 2). At first 10 microscopic fields per spleen section — each field representing approximately 5 sq. mm. of splenic tissue — were deemed sufficient for examination. A study of 200 fields from 10 different parts of 1 spleen, however, demonstrated that the variation from field to field might be considerable and that measurements of 20 fields from each case were required to furnish reliable averages. Like Hellman, we found no irregularities of malpighian follicle distribution in the sections of the spleen more extensively studied. It was hoped at first that this study could be based on 500 cases, but the extra material and labor that was required for the more intensive study of each case, together with a necessarily restricted time element, has limited us to 300 spleens. In most of the age groups, however, a satisfactory number of cases has been afforded, though

at the two extremes of life larger numbers would have been useful. In some of the earlier sections studied the small amount of tissue available did not permit a 20-field study — an unavoidable defect in the material. We of course recognized that our results might be unduly influenced by the cases that were studied over the smaller areas. To control this possibility the mean percentages of the

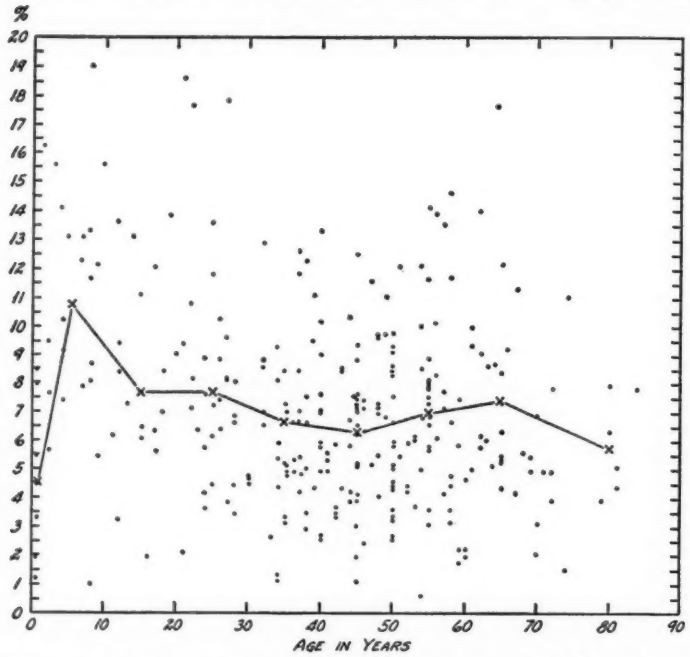

Chart 1. "Net" percentages of lymphatic tissue in the malpighian follicles at different ages in 300 cases of violent death. Dots indicate individual cases and curve of the mean for each decade.

10-field cases were combined with the 20-field cases "weighted" so that the latter had twice the value of the former. The resultant curve was so closely parallel to the unweighted curve, however, that the latter was adopted without further ado.

Results

The individual "net" percentages of lymphatic tissue, obtained as described above in the 300 cases, have been charted individually and a mean curve drawn for the 9 age groups (Chart 1).

This curve shows that, as in Hellman's series, the percentage of lymphatic tissue as studied by us is small in infants (4.5 per cent), but quickly rises to a maximum in the 1st decade (10.8 per cent). This was reached about 10 or more years earlier than the age of maximum weight of the spleen, as found both in this and in our earlier study.[1] The curve then drops sharply to 7.7 per cent in the 11 to 30 age groups, tending to fall gradually in the next 2 age groups. After a slight rise in the 2 age groups from 50 to 70

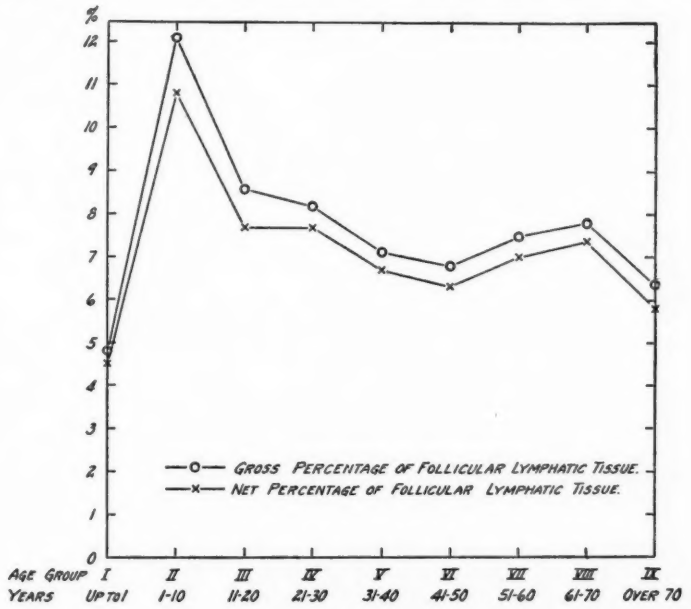

Chart 2. "Net" and "gross" percentages.

years, it falls in the last group (comprising all cases over 70) to 5.8 per cent. When studied statistically in terms of the standard error and regression coefficient, it is found: (1) that the peak at the 1 to 10 year period is significantly higher than the level of the period on either side. (2) If the groups from 11 years on are considered, the regression coefficient shows that the line is not significantly different from horizontal, though it does have a slightly downward trend. (3) If the regression line is considered in three parts (*i.e.*, from 11 to 50 years, from 41 to 70 years, and from 70

TABLE I

Data on the Lymphatic Tissue of Malpighian Follicles at Different Ages in 300 Cases of Violent Death

Group	Age	Number of cases	Net percentage ± 2SE	Gross per cent	Weight of follicular lymphatic tissue	Ratio: Follicular lymphatic tissue weight / Body weight	Number of malpighian follicles 2SE
	yrs.				*gm.*		
1	Up to 1	7	4.5 ± 2.0	4.8	0.36	0.00019	5.6 ± 0.62
2	1–10	22	10.8 ± 1.8	12.1	6.7	0.00030	4.2 ± 0.44
3	11–20	18	7.7 ± 1.6	8.6	10.6	0.00019	3.5 ± 0.44
4	21–30	36	7.7 ± 1.2	8.4	10.6	0.00016	3.2 ± 0.24
5	31–40	54	6.7 ± 0.8	7.1	8.5	0.00014	3.3 ± 0.34
6	41–50	68	6.3 ± 0.6	6.8	9.0	0.00012	3.0 ± 0.22
7	51–60	53	7.0 ± 1.0	7.5	9.2	0.00013	3.3 ± 0.42
8	61–70	29	7.3 ± 1.0	7.8	8.9	0.00014	3.9 ± 0.54
9	Over 70	13	5.8 ± 1.2	6.3	5.7	0.00010	2.8 ± 0.54

years on), three limbs result. The first of these is significantly downward, the second significantly upward and the third significantly downward. With proper regard for the above items 2 and 3, it can only be said that there is a definite suggestion of an increase in lymphatic percentage at ages 50 to 70, followed by a definite decline. This increase is not sufficiently marked, however, to rule out the possibility that it is merely an irregularity in a trend of a curve which from 11 years on is gently but steadily downward.

By subtraction of the "net" from the "gross" percentage of lymphatic tissue in the 9 age groups (Chart 2), figures can be obtained for the not inconsiderable areas occupied by the "central arteries" and the "pale centers." Although the effort was not made to separate these two factors and although there is still controversy as to whether "pale centers" represent lymphopoietic or reticuloendothelial tissue, or both, yet the higher percentages for the combined areas in early life are suggestive of greater lymphopoietic activity at that period — a finding already reported by earlier writers. It is hoped that this matter can be studied in proper detail in the near future and perhaps more light thrown on this phase of the ageing of splenic lymphatic tissue.

When the absolute weight of the lymphatic tissue in the malpighian follicles is estimated by multiplying the individual percentages of lymphatic tissue by the spleen weights, a somewhat different situation is encountered (Chart 3). The maximum sharp peak shifts from the 2nd group (1 to 10 years) to the 3rd and 4th groups (11 to 30 years), and the low secondary peak, which was present in the 7th and 8th groups (51 to 70 years) in the per cent chart, is modified by an increase also in the 6th group (41 to 50 years), so that this part of the curve suggests a maintenance or even a slight increase of splenic lymphatic tissue from 30 to 70 years.

Estimation of the ratio of the means of the absolute weight of the lymphatic tissue of the malpighian follicles to the means of the body weights (Chart 3) results in a curve much like that of the percentage of lymphatic tissue (Chart 1), except that the peak in the 1st decade is more marked. This, like the absolute weight estimates, then, tends to support the suggestion that there may be a later increase of lymphatic tissue — absolute as well as relative

— in the spleen lasting till old age, though it is still far from being statistically proved.

The number of malpighian follicles per unit area was found to be greatest in the 1st year (actually the first 3 months after birth) *i.e.*, a mean of 5.6 follicles per unit microscopic field (see Chart 3). These follicles, however, were very small, as must be the case in view of the low lymphoid percentage found at this period. The number of follicles per unit area decreased in each group to the age

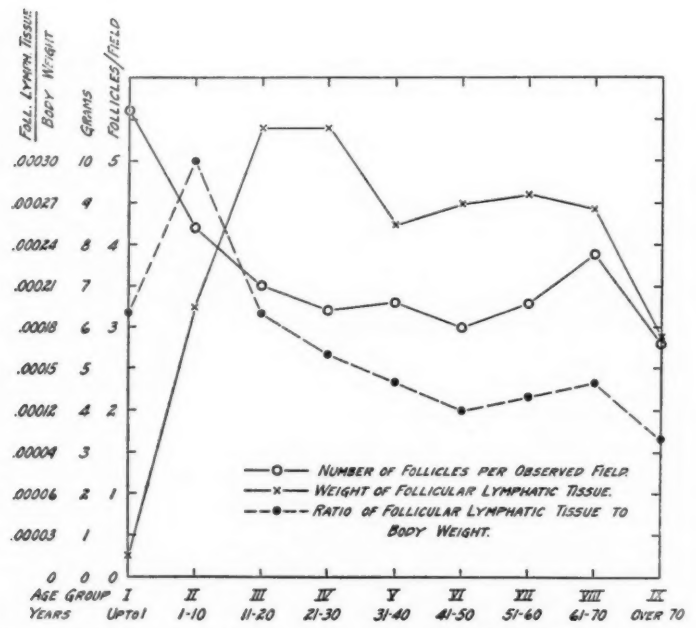

Chart 3. Weight of lymphatic tissue in the malpighian follicles, its ratio to body weight and the number of malpighian follicles.

of 30 (3.2 per field), then maintained a fairly constant level without significant changes, except for a rise in the 8th decade (3.9 per field) and a terminal drop (2.8 per field). These statements, of course, deal only with the concentration of follicles. It has not been possible to investigate their total number in the spleen at different ages; but in view of the much greater increase in the size of the adult organ than decrease in the number of follicles per unit

area, it is probable that their total number is also increased in the adult.

Comparison of the age, sex, color, mean spleen weight and mean body weight of these 300 cases with similar records of 2000 violent deaths (Krumbhaar and Lippincott [1]) brings out no significant differences. There is reason for regarding both series as not far from an average sample of the population in the eastern United States. In the smaller series, as is to be expected, there are more variations, but they are so unimportant that they will not be considered further.

Discussion

It will be seen that in our series each of the 6 adult groups up to 70 years of age contains 29 cases or more, and that there are 95 cases analyzed over 50 years of age, as compared with the 7 cases over 50 in Hellman's series.

In Hellman's series the percentage of follicular lymphatic tissue exhibited a steadier drop from the maximum than did ours, and showed higher values throughout (his Table 18). At least two factors in making our percentages smaller than those of Hellman are: first, the different points taken as the margin of the follicle; and second, the exclusion of central artery and pale reaction centers from the "net" areas. Consideration of our gross curve indicates that the second factor is of lesser importance. Hellman's curve for the absolute weight of the follicular lymphatic tissue (white pulp) is similar to ours in attaining a maximum later than the percentage maximum but differs in showing no tendency to the secondary increase in later life and again in having constantly higher values. We have not been able to determine that such unavoidable complications as shock or hemorrhage, or a rare mild infection or longer survival of a few days after the violence made any noticeable difference in the amount of lymphatic tissue of the cases we have studied.

The individual variation of the follicular lymphatic tissue at given ages is marked (Chart 1), as might be expected from the study of "normal" spleen weights previously reported,[1] and as found also in Hellman's lymphatic percentages. Unexpectedly low percentages are occasionally found in the younger age periods for which the most careful scrutiny, excluding such factors as

malnutrition, infectious disease, and so on, provides no explanation. Similarly, unexpectedly high percentages may be found in older life, though here the possibility of reaction to unobserved mild infection in some part of the body cannot be overlooked. Such marked individual variation, which lessens the value of statistical treatment of these figures, must apparently be ascribed to the unhelpful "individual idiosyncrasy." A wide normal range must be accepted; Hellman came to the same conclusion.

Summary and Conclusions

The amount of lymphatic tissue in the malpighian follicles of the spleens of 300 persons dying violent deaths has been studied at different age periods as part of a general study of the ageing of lymphatic tissue.

The percentage of follicular lymphatic tissue is small in infants but rises to a maximum in the 1st decade of life (*i.e.*, 10 or more years earlier than the whole spleen reaches its maximum weight). After a sharp drop in the next decade, a gentle fall in percentage occurs through the rest of life, with a suggestion of a second increase from age 51 to 70, followed by a distinct drop. No notable difference is found when this percentage is figured on the "net" (*i.e.*, excluding "central" arteries and pale centers) or on the "gross" basis.

The weight of the follicular lymphatic tissue (net per cent multiplied by the postmortem weight of the spleen) reaches a maximum later in life (11 to 30 years) than the per cent maximum, with a lower level maintenance (or even slight increase) until a final fall in the oldest age group.

The curve of the ratio of the follicular lymphatic tissue to the body weight is not strikingly different from that of the percentages.

Malpighian follicles are most numerous per unit area in early infancy, though small. They decrease in number to about the age of 30 years, then maintain a fairly constant number (except for an apparent rise in the 8th decade).

The combined areas of "central" arteries and pale centers are smallest in early infancy and greatest from 1 to 10 years. After decreasing through 3 decades, this area remains unchanged through the rest of life, perhaps because increasing thickness of the blood vessel walls compensates for a decreasing amount of pale centers.

Thus it can be said that the lymphatic tissue of the malpighian follicles in general behaves more or less like the lymphatic tissue elsewhere in the body at different ages. It differs from most of the lymphatic structures, however, in the sharp percentage decrease in the 2nd decade of life to a level that is fairly well maintained through the 7th decade, with even the suggestion of an increase in the 6th and 7th decades, while its absolute weight maintains its maximum through the 3rd decade.

NOTE: We are grateful to Messrs. M. S. Abel, J. D. Bibb, and W. H. Kety of the second year class in this medical school for their aid in outlining and measuring malpighian follicles, and especially to Mr. Abel for his advice and assistance in the statistical phases of the study.

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MULTIPLE NECROSES OF THE SPLEEN (FLECKMILZ)*

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"Multiple necroses" of the spleen is a descriptive term ascribed in the literature to a peculiar, characteristic gross appearance of the organ in which there occur multiple, large and small, bizarre shaped, map-like or rounded areas of firm, yellowish to grayish white necroses. These occur as isolated changes or are connected with one another and have infarct-like borders. In contrast with the ordinary embolic infarction of the spleen multiple necroses have been observed only infrequently. A survey of the literature would suggest that they are of varied origin.

An impetus was given to the study of this occurrence by Feitis [1] in 1921 who reported 2 cases and called the condition "Fleckmilz," or speckled spleen. The widespread interest created by this article has resulted in the report in the literature of 27 cases up to the present time. It is of interest that all of the spleens were encountered at autopsy and there was no suspicion clinically of the true process present since no pathognomonic signs or physical symptoms were noted.

Because of the current interest in the entity and the comparative rarity of reports in the literature of multiple necroses of the spleen, the following 2 cases are placed on record. Each of these differs etiologically from the cases reported by Feitis.[1] There is included, also, a comparison of the cases reported from a clinical, etiological, and pathological standpoint, in so far as generalization of a few cases permits.

Case Reports

Case 1. J.J.B., a white male, aged 17 years, was admitted to the medical service of the John Gaston Hospital Nov. 28, 1936, complaining of general malaise, severe headaches and chilly sensations of 8 days duration. Two days following the onset of illness he experienced a severe chill and began passing dark brownish urine, which continued for 3 days. The symptoms of headache and malaise continued with high fever, nausea and weakness.

Physical examination revealed a well developed and nourished white male

* Received for publication May 14, 1938.

who was somewhat disoriented as to time and place. The temperature was 102° F., pulse 140 and respirations 20 per minute. The blood pressure reading was 122/40. There was an icterus of the skin and a generalized lymphadenopathy. No other abnormality was noted.

Laboratory examination revealed a red blood cell count of 1,260,000, white blood cells 6950, and hemoglobin 4 gm. per cent. Differential study showed a lymphocytosis. The urine was alkaline and cloudy with a specific gravity of 1.010, 3 plus albumin, and 3 to 6 granular and hyaline casts per high power field. The Kahn blood test was negative. Blood smears examined for malaria were negative. Blood cultures were positive for *Bacillus paratyphosus B* on repeated examination.

The clinical course continued to indicate a septic condition with the temperature varying between 99 and 105° F. Delirium became more marked, supportive treatment was of no avail, and the patient died Dec. 3, 1936, on the 6th day of hospitalization.

Postmortem Examination

Autopsy was performed 2 hours following death and revealed a well developed and nourished, anemic, jaundiced young white male. Examination of the brain showed numerous, tiny, 1 up to 3 mm. sized petechiae within the substance of the cerebral cortex. On microscopic examination these were found to be small capillaries occluded by thrombi and surrounded by hemorrhage. The lungs were firmer than normal and oozed copious amounts of straw colored fluid from congested sectioned surfaces. The remaining viscera revealed parenchymatous degeneration.

In gross the spleen offered a startling picture, being enlarged to 740 gm. The splenic vessels at the hilus had smooth linings and contained fluid blood. The organ was soft in consistence, smooth for the most part, and was violacious in color. Beneath the capsule there were visible multiple, slightly raised, irregular, rounded or map-like, pin-point up to 3.5 cm. sized, gray to grayish yellow areas surrounded by a broad zone of hemorrhage (Fig. 1). On section the picture was enhanced on a dark red background. The infarcted areas were diffusely distributed through the splenic pulp, presenting a mosaic pattern of isolated and confluent necroses. The larger areas were often connected by narrow bands of a similar necrotic appearing tissue. The smaller areas were isolated. The changes were most marked toward the periphery of the spleen, although they were present irregularly throughout, seeming to affect selectively no particular portion. Cultures from several regions of the tissue revealed *Bacillus paratyphosus B.*

Microscopic Examination

In the spleen it was seen that the grayish white areas represented necrotic splenic pulp in which the outlines of tissue elements could still be recognized. These anemic infarcts were fresh and were large or small in size, often connected by bridges of necrotic tissue with normal intervening splenic tissue. In the larger areas of necrosis the centers showed a pale, eosin staining, homogeneous material. A fine nuclear dust was found to be abundant, particularly with the Heidenhain-van Gieson stain. With this stain a fairly well preserved trabecular and reticular network was demonstrated. Numerous small clumps of bacteria were present (Fig. 2). Occasionally seminecrotic blood vessels were seen, frequently filled with fresh thrombi. At the periphery the tissue was found to be better preserved and was infiltrated with lymphocytes, large mononuclear phagocytes and a few polymorphonuclear leukocytes. This zone merged into a surrounding broad area of hemorrhage. In the smaller zones and in areas in which the degeneration was not so advanced, as well as in the connecting bridges between the larger foci, the above described distinct zones could not be made out. In these latter areas many intact cells were visible, the pulp was seminecrotic, and cells with pyknotic and karyorrhetic nuclei were also seen. In the non-necrotic tissue the pulp was normal. The sinusoids were empty or distended with well preserved red blood cells, lymphocytes and phagocytic mononuclear cells containing iron pigment and a few leukocytes. The germinal centers in the non-necrotic regions showed moderate hyperplasia. The distribution of the necroses suggested that there was no selective involvement of the malpighian bodies. Often a middle sized or smaller artery was seen to contain a thrombus. The trabecular and follicular arteries infrequently showed thrombotic occlusion. Interstitial fibrosis or an increase in reticulum was not observed.

Anatomical Diagnoses: Bacillus paratyphosus B septicemia with embolic phenomena in the brain and spleen (Fleckmilz), pulmonary edema, and parenchymatous degeneration of viscera.

CASE 2. Mrs. H.C., a white female, aged 20 years, was admitted to the Evanston Hospital, Chicago, Ill. on March 22, 1930, complaining of having had an abscessed right upper molar tooth for 1 year. This lesion was accompanied by swelling and tenderness of the gums, and later there had been evidence of Vincent's angina. She had slowly but progressively lost weight,

was easily fatigued, and often suffered nausea and abdominal distress following meals. For 5 days prior to admission she had experienced a nocturnal rise in temperature, which subsided each morning. The family and past histories were irrelevant.

Physical examination showed that the temperature on admission was 100° F., and thereafter septic in type, varying between 99 and 106°. The pulse fluctuated between 84 and 150 per minute. Respirations were 18 up to 30 per minute. The patient was undernourished, anemic and jaundiced, and showed evidence of recent loss of weight. The gums over the right upper molar teeth were swollen, tender and ulcerated. The pharynx showed catarrhal hyperemia. The heart and lungs were normal. There was tenderness in the upper abdomen over the region of the spleen and liver.

Laboratory examination revealed red blood cells to be 2,300,000, white blood cells 8000 and hemoglobin 40 per cent. The differential count showed 46 per cent polymorphonuclear neutrophilic leukocytes and 54 per cent lymphocytes. Blood cultures were negative. Cultures from the abscessed molar teeth revealed *Streptococcus viridans*. Smears from the same region showed abundant *Borrelia vincenti*, together with a fusiform bacillus.

During the clinical course repeated transfusions and supportive measures were of no avail. The septic condition continued progressively worse until death on April 8, 1930, on the 16th day of hospitalization.

Postmortem Examination

The body was well developed but undernourished. Pallor and icterus of the mucous membranes were noted. Multiple petechial hemorrhages occurred in the skin over the chest and abdomen. An ulcer was found in the swollen gums along the buccal margins of the right upper molar teeth. The serous cavities contained a slight excess of clear, straw colored fluid. The lungs showed evidences of edema and terminal bronchopneumonia. The remaining viscera revealed parenchymatous degeneration, with the exception of the spleen.

In gross the spleen was markedly enlarged and weighed 918 gm. Through the capsule, and particularly on section, one could see the red pulp studded with multiple, small and large, up to 1 cm. in diameter, irregularly rounded, firm, dark red opaque areas, and one large, map-like grayish yellow area surrounded by a zone of bright red and measuring 4.5 by 1.5 cm. (Fig. 3).

Microscopic Examination

The larger grayish yellow infarct was similar in appearance to those described in Case 1, with a few additional features. The area of necrosis showed a rather marked tendency toward fibrous tissue organization, being particularly prominent in the surround-

ing hemorrhagic zone, as shown by the van Gieson stain. More centrally there was newly formed fibrous tissue. The trabecular and reticular network showed degeneration in the central portion of this larger anemic infarct. Many larger, as well as middle and smaller sized blood vessels showed thrombi with a tendency toward organization (Fig. 4). The smaller areas of tissue necrosis, however, presented the picture of hemorrhagic infarct and appeared to be of more recent origin. In the necrotic portions there was massive hemorrhage both within and without the confining sinusoids so that the splenic tissue for the most part was obscured. The malpighian bodies were made out with difficulty. Culture of splenic tissue showed *Streptococcus viridans*.

Anatomical Diagnoses: Abscessed molar teeth with *Streptococcus viridans* septicemia, multiple necroses of spleen (Fleckmilz), anemia, jaundice, pulmonary edema and bronchopneumonia.

Comment

The above described cases showed a bacterial thrombotic occlusion of the splenic vascular system with resultant multiple infarcts of the organ. These necroses were of a size and distribution varying with the anatomical method of division of the blood vessels as well as the size of the vessel haphazardly the site of a thrombus. The gross appearance of the spleens was similar to the multiple necroses described in the cases of Feitis, but had a different etiological factor. The other cases reported in the literature showed a varied causation but had a similar microscopic appearance.

Discussion

Various writers on the subject of Fleckmilz have at different times attempted to divide or classify the cases reported on the basis of the essential lesion which brings about the necroses. The origin of the necrosis *per se* may be explained in one of three ways, namely closure of the vessel to a designated region of tissue, relative vascular insufficiency with superimposed tissue injury, or pure tissue injury which by accident was situated in the region supplied by the individual vessel. The cases which have been described may arbitrarily be divided into the groups listed in Table I.

All cases reported listed in Table II show the group into which

they may be placed, as well as a comparison of the basic anatomical changes that brought about the infarcts.

Nineteen cases are observed to be similar to those originally described by Feitis [1] and are associated with renal insufficiency. He ascribed the necrosis to arterial damage superimposed upon an arteriosclerosis. The lesions affected primarily the smaller middle sized arteries and consisted of hyaline and fatty degeneration with intimal proliferation and often subsequent thrombosis. Lubarsch [7] directed attention to the additional factor of the toxin liberated in uremia and renal insufficiency with which these cases were associated. He believed, therefore, that in his 3 cases the thrombosis was due to an autointoxication. The toxin acted upon the arterio-

TABLE I

Multiple Necroses of the Spleen (Fleckmilz). Groups into which Reported Cases may be Divided

Group	Number of cases
1. Arteriosclerotic toxic-thrombotic	19
2. Angiospastic toxic-thrombotic	2
3. Purely toxic	3
4. Arteritic	1
5. Infectious toxic-thrombotic	4
Total	29

sclerotic, relatively inefficient vessels to produce thrombosis. Meuret,[5] Hosoi,[8] Nicod,[9] Klemperer and Otani,[10] Adolphs,[11] Spier,[12] Rake,[13] Laufer,[14] and Guttman [15] agree with this view and cite cases in point.

Geipel [2] and Matthais [3] individually studied spleens with extensive isolated and aggregated infarctions in which there was considerable arterial and venous thrombosis, but in which the vessel walls were normal. The organs were from patients who died from eclampsia. They agreed with Beneke's idea (quoted by Matthais) of the origin of organic injuries through angiospasm caused by the hypothetical eclampsia toxin and followed by secondary thrombosis. These, then, are classed as the angiospastic toxic-thrombotic group.

Enzer,[6] Lubarsch,[7] and Magnus [16] each described spleens from individuals who suffered from profound anemia but no changes were noted in the blood vessel walls, either thrombosis or degener-

TABLE II

Multiple Necroses of the Spleen (Fleckmilz). Cases Reported to Date

Author	Age	Sex	Spleen	Basic pathology	Group
	yrs.				
Feitis (1921)	39	M	205 gm.	Chronic nephritis, uremia, arteriosclerosis	1
Feitis (1921)	60	M	8 x 4.5 x 1.5 cm.	Chronic nephritis, arteriosclerosis	1
Geipel (1924)	35	F	330 gm.	Eclampsia, renal cortical necrosis	2
Matthais (1924)	..	F	..	Eclampsia, renal necrosis, brain hemorrhage	2
Meuret (1924)	31	M	12 x 7 x 4.5 cm.	Chronic nephritis, uremia	1
Meuret (1924)	46	M	..	Arteriosclerosis, renal insufficiency, brain hemorrhage	1
Wilton (1925)	31	F	650 gm.	Upper respiratory infection, empyema sphenoid	5
Enzer (1926)	59	F	9 x 5 x 3 cm.	Pernicious anemia	3
Lubarsch (1927)	44	F	105 gm.	Generalized arteriosclerosis, renal insufficiency	1
Lubarsch (1927)	52	M	130 gm.	Generalized arteriosclerosis, renal insufficiency	1
Lubarsch (1927)	..	..	215 gm.	Generalized arteriosclerosis, renal insufficiency	1
Lubarsch (1927)	51	M	..	Pernicious anemia	3
Hosoi (1928)	45	F	110 gm.	Chronic nephritis, arteriosclerosis, apoplexy	1

TABLE II (*Continued*)

Author	Age	Sex	Spleen	Basic pathology	Group
	yrs.				
Nicod (1930)	38	M	14 x 9 x 4 cm.	Chronic nephritis, uremia, arteriosclerosis	1
Nicod (1930)	48	F	250 gm.	Chronic nephritis, uremia	1
Klemperer and Otani (1931)	46	F	..	Chronic nephritis, uremia	1
Adolphs (1931)	33	F	..	Chronic nephritis, arteriosclerosis	1
Adolphs (1931)	57	M	..	Chronic nephritis, arteriosclerosis	1
Adolphs (1931)	11	F	..	Nephritis, uremia	1
Spier (1931)	51	F	92 gm.	Arteriosclerosis, renal failure, brain hemorrhage	1
Rake (1932)	44	F	140 gm.	Chronic nephritis, uremia	1
Laufer (1933)	58	M	13 x 7.5 x 5 cm.	Chronic nephritis, uremia	1
Laufer (1933)	37	M	15 x 8.5 x 4.5 cm.	Chronic nephritis, uremia	1
Laufer (1933)	26	M	15 x 15 x 12 cm.	Streptococcic septicemia, appendiceal abscess	5
Guttman (1934)	45	F	40 gm.	Arteriosclerosis, renal insufficiency, pneumonia	1
Magnus (1937)	21	M	600 gm.	Necrotizing arteritis	4
Magnus (1937)	63	M	300 gm.	Anemia, pneumonia	3
Schmeisser and Harris (1938)	17	M	740 gm.	*B. Paratyphosis B.* septicemia	5
Schmeisser and Harris (1938)	20	F	918 gm.	*Streptococcus viridans* septicemia	5

ation. These are the types that are probably due to pure tissue injuries which were by chance located in areas supplied by individual arteries, and the etiological factor is purely toxic.

Magnus' 2nd case yielded a surprise. No similar record can be found. He ascribed the tissue necrosis to a widespread acute necrotizing arteritis resembling somewhat periarteritis nodosa but in which there was an absence of periarteritic leukocytic infiltration and aneurysm formation. The necrosis was manifest, not only in the spleen but in the pancreas, kidneys and alimentary tract. This, then, exemplifies a type different from any other. It may be grouped as arteritic in nature.

Our 2 cases comprise still another group from the standpoint of etiology. They must be classed as due to infection with the possibility of the toxins liberated coming into play. Wilton's [4] description of a patient with empyema of the sphenoid sinuses, associated with an acute upper respiratory infection, probably belongs to this group. Laufer's [14] 3rd case was from a man who had a streptococcic septicemia incident upon an appendiceal abscess, and closely resembled our 2nd case.

Summary

1. Fleckmilz (Feitis [1]) is a descriptive term applied to the gross appearance of a spleen with multiple infarcts and necroses.

2. The cases subsequently reported in the literature have had a similar macroscopic appearance but have been of varied origin.

3. It is observed that the multiple necroses can be divided, etiologically and pathologically, into five groups.

4. We report 2 cases, which are classed in the infectious toxic-thrombotic group, the 1st showing anemic and the 2nd mainly hemorrhagic infarcts.

Note: We are indebted to Dr. W. W. Brandes for permission to use the 2nd case and to Dr. Joseph L. Scianni for the illustrations.

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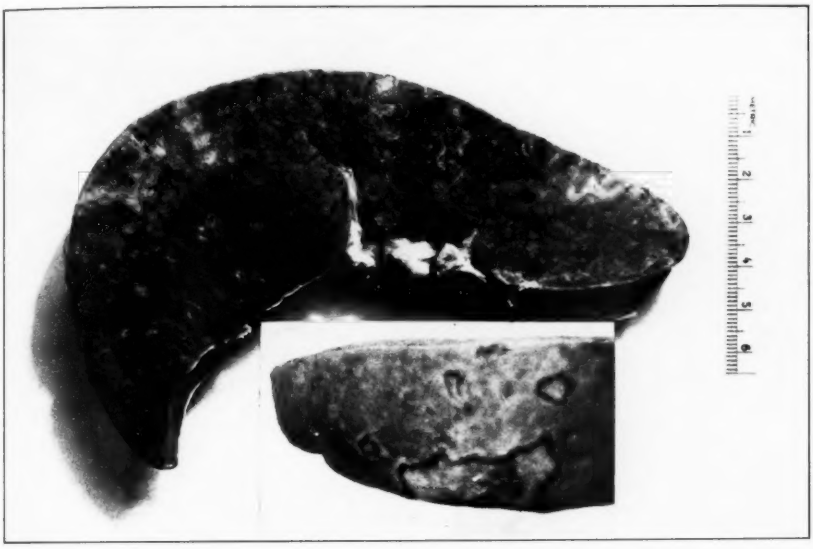
DESCRIPTION OF PLATES

Plate 152

Fig. 1. Case 1. Multiple necroses of the spleen (Fleckmilz). The enlarged spleen shows beneath its capsule and on section multiple, slightly raised, map-like, gray to grayish yellow areas surrounded by a broad zone of hemorrhage.

Fig. 2. Case 1. Multiple necroses of the spleen (Fleckmilz). Part of an anemic infarct is seen to the right, marginated by small clumps of bacteria and better preserved tissue infiltrated with many red blood cells and a few lymphocytes, large mononuclear phagocytes and polymorphonuclear leukocytes. At the left is the living capsule. Microphotograph × 200.



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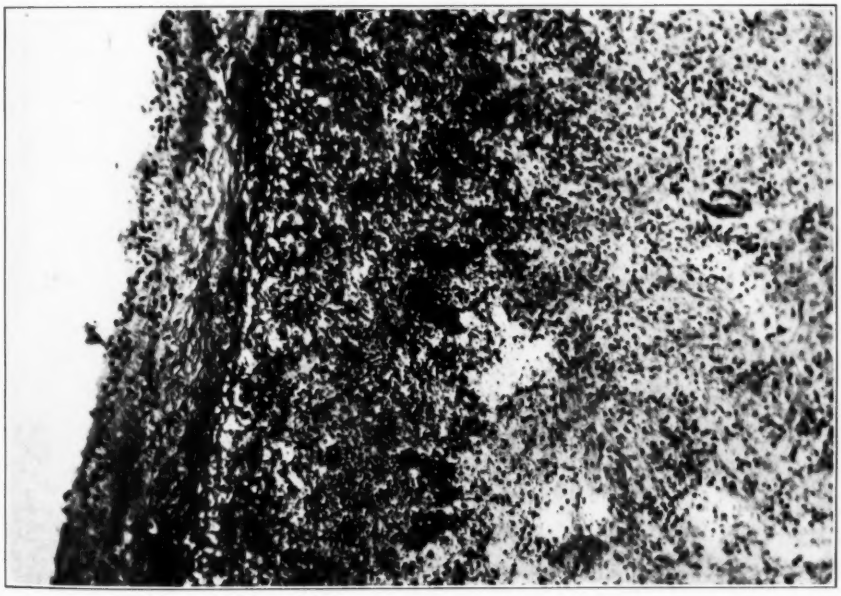


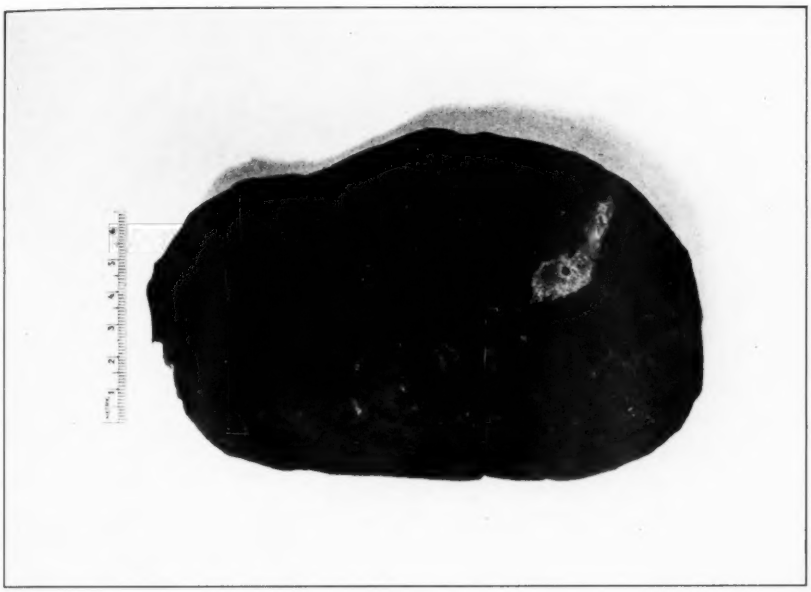
2

Schmeisser and Harris Multiple Necroses of Spleen

PLATE 153

FIG. 3. Case 2. Multiple necroses of the spleen (Fleckmilz). The markedly enlarged spleen seen on section is studded with irregularly rounded, firm, dark red opaque areas and one large, map-like, grayish yellow area surrounded by a red zone.

FIG. 4. Case 2. Multiple necroses of the spleen (Fleckmilz). Portion of a hemorrhagic infarct with the thrombosed artery is shown surrounded by living splenic tissue at the left. Microphotograph × 200.



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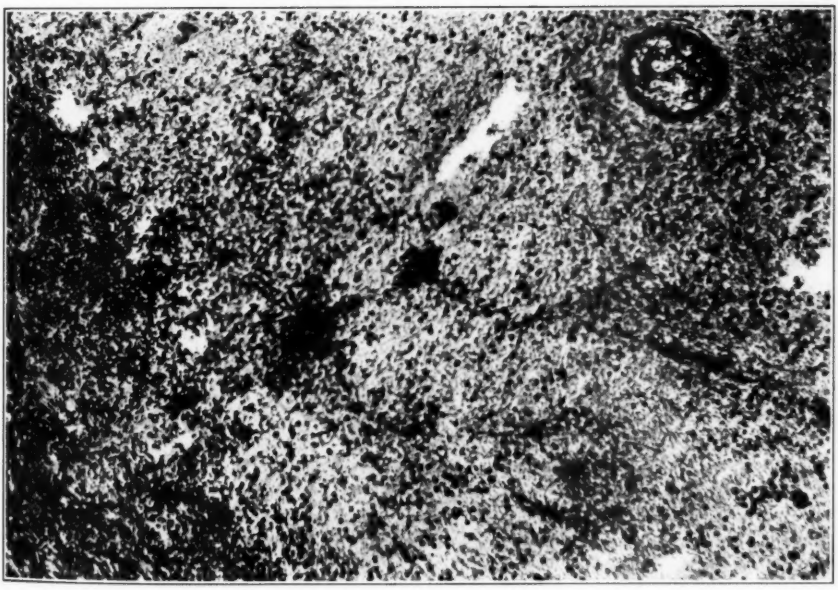

4

Schmeisser and Harris Multiple Necroses of Spleen

GIANT INTERSTITIAL CELLS AND EXTRAPARENCHYMAL INTERSTITIAL CELLS OF THE HUMAN TESTIS *

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The frequent presence of interstitial cells of the testis (Leydig cells) with 2 or 3 nuclei is often mentioned in the literature, but the finding of multinucleated giant interstitial cells with up to 20 and 30 nuclei has to my knowledge never been described or illustrated, although it has been vaguely hinted.

It is of interest that the original description of the interstitial cells by Leydig [1] in 1850 contains illustrations of binucleated cells. Von Winiwarter [2] in one of the classical papers on the histology of the interstitial cells illustrated an interstitial cell with 4 nuclei but did not discuss the number of nuclei and in fact mentioned it only as incidental to the increased number of centrosomes. Rasmussen [3] states that binucleated and even multinucleated cells have been described and uses von Winiwarter's figure as an illustration. Maximow [4] states only that cells with 2 nuclei are relatively common. Cowdry [5] says that 2 or even more may occur in a single cell. Oberndorfer [6] states that cells with 2 or 3 nuclei are often found and illustrates cells with 4 and 3 nuclei. Wieser [7] "not seldom" found cells with 2 and more nuclei, but said no more. In none of the above cited articles has the "and more" in connection with the number of nuclei been further elucidated. Stieve [8] comes the closest to mentioning a giant interstitial cell when he says that often one finds 2 and more nuclei lying close together in a mass of cytoplasm (Plasmabezirk), but he does not illustrate this. Nowhere, then, in the literature has anyone definitely spoken of or illustrated an interstitial (Leydig) cell of the testis with more than 4 nuclei.

With no very minute degree of searching I was able to find giant interstitial cells with 4 or more nuclei, up to as many as 30, in 85

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of 721 microscopically sectioned testes.* Cells with 2 and 3 nuclei were of course seen frequently, but these were not counted. The number of giant cells per testis varied from 1 in about 10 low power microscopic fields, which was considered the minimum number necessary to include the testis in this group, to about 10 in 1 low power microscopic field. The range of nuclear multiplicity was complete; that is, cells could be seen with 4, 5, and so on, up to 10, 15, 20 or 30 nuclei; the number most frequently seen was 8 or 10. Nuclear division, mitotic or amitotic, was not seen. In about six instances cells with 3 or 4 nuclei were seen among the extraparenchymal interstitial cells in the tunica albuginea and hilus testis, and one cell with 8 nuclei (Fig. 4) was seen here. Neither giant nor ordinary interstitial cells were seen in the epididymis.

These giant cells are excellently illustrated in the microphotographs (Figs. 1, 2, 3 and 4). They occur both isolated and in the midst of small groups of mononuclear interstitial cells, from which they are unquestionably derived. They are usually oval and measure up to about 50 by 80 . The nuclei, grouped more or less in a semicircle at one or both ends of the cell, are usually identical with those of the mononuclear interstitial cells, but often in the larger cells (Figs. 2 and 3) they are smaller, darker and more wrinkled. One fairly prominent nucleolus is usually seen. The cytoplasm is eosinophilic and somewhat granular. A short distance in from the border of the cell, between and inside of the nuclear semicircles or masses, is a zone of brownish orange pigment similar to that in the mononuclear cells; inside this is an oval or spherical center zone of clearer cytoplasm (Figs. 1, 3 and 4). Reinke crystals were observed rarely in cells with 4 nuclei, but not with higher numbers (they were found, without special search, in the ordinary interstitial cells of about 40 of the 721 testes).

Whether these giant cells form from fusion of several preexisting single cells or by nuclear division and enlargement of one cell could not be determined. There appears to be no correlation

* The 721 testes which formed the basis of this study were obtained from 470 routine autopsies on persons 18 years of age or older, performed by myself or other members of the Department of Pathology of the University of Minnesota. The primary object of the study was to determine the changes in the weight and histological structure of the adult testis with age and in various diseases. As study of the microscopic sections progressed I was impressed by the frequent occurrence of giant and extraparenchymal interstitial cells.

with age; in the age group 18 to 40 years they were found in 8 testes; 41 to 66 years, in 58 testes; and 67–88 years, in 19 testes. These figures correspond fairly well with the age distribution of the entire series. They were found in all types of disease conditions — 21 cases of acute conditions, 54 of chronic non-malignant, and in 10 malignant. Here again there is no great variation with the distribution of the entire series. As can be seen from the illustrations there is little resemblance between the giant interstitial cells and Langhans giant cells; any possible relationship should, however, be discussed. Of my total material of 470 cases, 16 had tuberculosis as the chief cause of death. Four of these 16 cases showed tuberculous epididymitis; 2 of these 4 also showed tuberculosis in the testis; none of the 4 had giant interstitial cells, although many of the usual (Langhans) giant cells were present. Giant interstitial cells were seen in 3 of the 16 cases with tuberculosis as the chief cause of death, but none of these 3 showed tuberculous involvement of either epididymis or testis.

It was my impression that the giant interstitial cells tended to be present with the more moderate increases in the numbers of the ordinary interstitial cells rather than with massive numbers of the latter or with the normal small quantity. Of the 85 testes showing giant interstitial cells, ordinary interstitial cells of what I chose to call Grade 0 or normal (roughly 50–150 per sq. mm.) were present in 15 per cent, Grade 1 (slightly increased or roughly 150–400 per sq. mm.) in 60 per cent, and Grade 2 (moderately increased, or about 400–1000 per sq. mm.) in 22 per cent. This compares with 40, 43 and 13 per cent respectively for the entire series of 721 testes. The highest degrees of increase, Grades 3 and 4, were present in 3 per cent of the testes with giant cells and in 4 per cent of the entire series. The giant interstitial cells did not tend to be present with severe atrophy; otherwise no definite relation to either diffuse or focal atrophy could be observed.

Extraparenchymal Interstitial Cells

Knowledge of this type of cell, occurring in both the testis and the ovary, is quite recent. These cells have hitherto usually been described under the term "sympathicotropic cells." The first accurate description, the name "sympathicotropic," the first mention of their occurrence in the testis, and their first comparison

with the interstitial cells of the testis, was given in 1922 by Berger,[9] who since then has written the most on this subject. Berger's findings received confirmation in the American literature in 1927 by Brannan,[10] who studied chiefly the ovary, but also found similar cells in 6 testes. Several European authors have confirmed Berger's findings, although some question his interpretations and conclusions.

Berger [9] described the "sympathicotropic" cells as small or large masses of cells intimately associated with the non-medullated nerves of the ovary and testis. The cells were large, polymorphic and acidophilic, with a finely reticulated nucleus and a large nucleolus; the protoplasm was granular or else compact in the center and clear or foamy at the periphery. The cells were in intimate relation with nerve fiber bundles and sometimes within them; they were also in intimate relation with capillaries. They sometimes contained brown pigment, or crystalloids similar to those in the interstitial cells, or doubly refractile alcohol-soluble lipoids. They were not chromaffin cells but showed what Berger called an attenuated chromaffinity; some of the cells had a natural light brown tint and this became more intense after chromation. Berger later modified this statement concerning chromaffinity. The morphology of the cells in the testis was similar to those in the ovary.

In the testis Berger found the cells around the nerves near and in the testis and in the tunica albuginea, but not in the epididymis. At certain points he found these cellular masses to be continuous with the regular interstitial cells of the testis and having identical morphology. A second important finding was that the variations of the "sympathicotropic" cells paralleled those of the interstitial cells with regard to number, pigmentation, crystals, and so on.

Berger's excellent morphological studies were somewhat overcast by the endocrinological implications he gave to these cells. In his 1922 publication he concluded that these cells were a part of the "interstitial gland" of the testis, following the ideas of Bouin and Ancel [11]; he gave to the cell masses in the ovary the provisional name of "sympathicotropic gland of the hilus of the ovary," and considered it the homologue of the "interstitial gland" of the testis. Berger's 1928 and 1930 publications [12, 13] essentially restated his previous findings, and the latter also contained a rather speculative consideration of the "neurocrine" function of the cells

which need not concern us here. In 1932 Berger published [14] a résumé of the literature, pro and con, to that date; by this time he had also concluded that the "sympathicotropic" cells of the testis were purely and simply Leydig cells, entirely different from chromaffin (paraganglionic, pheochrome) cells, although formerly he had thought that they had some of the features of both. In the interim some opposition to Berger's views had appeared, chiefly from de Winiwarter [15] who considered these cells to be chromaffin cells.

De Winiwarter (the name is sometimes spelled von Winiwarter) had previously, in 1911, described pheochrome cells in the hilus of the ovary and testis of the fetus and the newborn. After Berger's publication he investigated the adult ovary and reached the same conclusions as previously concerning the fetus and the newborn. Berger's preparations and illustrations, he thought, merely confirmed his own previous work instead of dealing with a different type of cell. He saw no crystalloids and thought that these cells had but a superficial resemblance to Leydig cells; he admitted that he had been unable to obtain the chromaffin reaction. The great difficulty in de Winiwarter's reasoning, however, is that Berger had stressed the resemblance of the "sympathicotropic" cells to the interstitial (Leydig) cells of the adult testis, and de Winiwarter stated that he had not examined the adult testis but was sure the same findings would hold good there as had in the fetus and newborn.

Brannan's paper,[10] appearing in 1927, is of considerable interest in that it appears to be the only one in the American literature dealing with the "sympathicotropic" cells (all of Berger's publications have been in French and German journals). Brannan studied chiefly the cells in the ovary, but he did find small nodules around non-myelinated nerves in the hili of 6 testes. In the main he agreed with Berger that chromaffin and argentaffin reactions were negative, that the cells contained lipoids, pigments and crystals, that they always occurred in small groups in and near the hilus of the ovary or testis, and that their chief feature was their constant association with nerves. Brannan stated that their association with nerves, together with the known fact that chromaffin (pheochrome) cells did occur in the testicular and ovarian hili, would lead one to suspect that the "sympathicotropic" cells would also possess

chromaffinity, but he could not demonstrate it. He also stated that the cells appeared to be epithelial in nature but not glandular. Brannan made no mention of the regular interstitial cells of the testis in connection with the "sympathicotropic" cells.

Kohn [16] also confirmed Berger's findings and stated that in both the ovary and the testis these cells had all the attributes of Leydig cells — lipoid, pigment, Reinke crystals — and that in the testis their number and characteristics paralleled those of the Leydig cells. Pawlowski,[17] who studied only the ovary, took an attitude intermediate between Berger and de Winiwarter; he considered that these cells were not chromaffin cells but, because of their intimate connections with nerves, were functionally connected with the sympathetic system. He proposed that they be named "hilus cells" or "Berger's hilus cells." Neumann [18] also studied only ovaries and more or less agreed with Berger.

The most detailed morphological description of these cells in the testis is by Wieser [7] who studied some 132 cases of all types and ages. Within each age group and each type of disease he found wide fluctuations and could come to no definite conclusion in respect to these features; the important fact was that point for point the "hilus" or "sympathicotropic" cells were identical with the regular interstitial cells.

Finally, Berger, in order to overcome the objection of de Winiwarter that Berger's cells were chromaffin cells, published in 1935 [19] a report of a testis from a newborn containing both chromaffin and "sympathicotropic" cells.

Extraparenchymal interstitial cells have been mentioned at various times, without any reference to their association with nerves, or to being any different from the ordinary interstitial cells. Berblinger,[20] Priesel,[21] and Harms [22] have mentioned the finding of groups of interstitial cells in the hilus of the testis, the tunica albuginea, or some location other than their usual one. Stieve [8] in von Mollendorff's Handbuch states that in adults there are not infrequently found in the tunica albuginea small groups of interstitial cells, and that crystalloids may be found in these. Stieve [8] and Brack [23] picture such cells.

In summary it may be said that within the last 15 years there has been described, chiefly by Berger but confirmed by a number of other investigators, the frequent presence of masses of cells in

the testicular and ovarian hili having intimate connection with the non-medullated nerves and having in both the ovary and the testis all the characteristics of Leydig cells with fluctuations paralleling the latter in the testis.

Personal Observations: Early in the study of the microscopic sections of this series of testes, and before becoming acquainted with the literature on the "sympathicotropic" cells, I was impressed by the same sort of findings as described by Berger and others. To anticipate, I may now say that my findings agree in all respects with those of the majority of writers on the subject, with the exception that these extraparenchymal interstitial cells occur not only in the hilar region of the testis but at any point within the tunica albuginea, whether distant from the hilus or not. (When referring to "within the tunica albuginea" I mean that the cell groups are entirely within the tunica and not merely invading its innermost laminas, as can be seen in almost any testis with numerous interstitial cells). Because they may be found at a distance from the hilus as often as not, the name "hilus cells" as proposed by Pawlowski is inappropriate. The name "sympathicotropic" under which they have heretofore usually been designated implies a functional status which is not proved. I therefore propose the name "extraparenchymal interstitial cells" or "extraparenchymal Leydig cells."

Of the 721 microscopically sectioned adult testes in this series, the tunica albuginea had been removed in 240 for ease in sectioning. In the remaining 481 there were groups of extraparenchymal interstitial cells in connection with nerves in the hilus or tunica albuginea in 109 testes, and the same cells not in connection with nerves in 85 testes; 45 of these 194 testes were duplicates, that is, cells both associated with and not associated with nerves were found in the same testis. In the 85 cases where masses of these cells were seen without immediately adjacent nerves it is believed that a sufficient number of adjoining sections would show their relation with nerves in the majority of cases, although probably not in all. For example, in some cases where the paraffin ribbon for one type of stain had not been taken immediately adjacent to that for another stain, but at some distance (say 100 μ) away, it was noted that one section would show the nervous connection and the other would not with the same group of cells.

Of the 149 testes that showed groups of cells in the hilus and tunica albuginea, either associated with nerves or unassociated, or both, 29 per cent showed ordinary interstitial cells of Grade 0, 42 per cent of Grade 1, and 24 per cent of Grade 2; this compares with 40, 43 and 13 per cent respectively for the entire series. I agree in general with the statements in the literature that when the ordinary or parenchymal interstitial cells are numerous, so are the extraparenchymal cells, although this is not always the case. I also agree as to the general similarity of the two in regard to morphology, pigmentation, crystals, and so on. Of the 149 testes with extraparenchymal interstitial cells, 21 showed pigment (Fig. 6) and 9 Reinke crystals (Fig. 7). Occasional multinucleated (2, 3, 4, and one with 8 nuclei) extraparenchymal interstitial cells (Fig. 4) were found. In my material they were, in agreement with the literature, found in all ages from 18 to 88 years.

One point must be remembered in regard to the stated frequencies of finding the extraparenchymal interstitial cells and that is that even in a midsagittal section of the testis with the tunica albuginea and hilus complete, the relative proportions of the latter that are sectioned as compared to those remaining unsectioned is very small, and therefore there must be numerous cases where these cells would be shown in serial sections but not in one or a few sections.

The size of the groups of extraparenchymal interstitial cells in my material varied from a few cells (which, of course, may have been the edge of a larger group) to masses which, including the enclosed nerve bundles, were 1.5 mm. in diameter (Fig. 5). The usual size of group found is shown in Figure 6. Very frequently, as mentioned in the literature, the cells were intraneural as well as perineural. There was no site of predilection for the cell groups. Previous writers have mentioned their occurrence chiefly in the hilus or rete testis, saying little about the tunica albuginea. In my material they were actually more frequent in the albuginea, because of the greater bulk of tissue, and relatively these cells could be found almost as frequently at any point within the albuginea, even directly opposite the hilus, as in the hilus. Previous writers have mentioned that these cells never occur actually within the epididymis, and neither did I find them there. Berger has found them along the spermatic cord as far as 6 cm. away from the testis.

These cells, again in agreement with the literature, are to be found in and around the intertubular as well as the paratesticular nerves, but with greater difficulty (except just inside the tunica albuginea, where they can readily be seen). There are two reasons for this: the nerves within the testis are smaller and because of the multiplicity of tissues in the interstitium are more difficult to observe. However, this perineural relationship can be observed within the testis, especially after tubular atrophy has taken place and the nerves stand out more sharply.

Summary

1. In a study of the microscopic sections of 721 testes from a series of 470 autopsies on males 18 years of age or more, giant interstitial (Leydig) cells having from 4 to 30 (usually 8 or 10) nuclei were found in 85 testes. They were found at all ages and in all sorts of general disease conditions. They do not appear to have been previously described, although their existence has been hinted at.

2. The observations of Berger and others on the "sympathicotropic" or "hilus" cells have been confirmed and extended. It is generally agreed that these cells in the testis are identical with the ordinary interstitial or Leydig cells. I have proposed the name "extraparenchymal interstitial cells" or "extraparenchymal Leydig cells" as best describing them.

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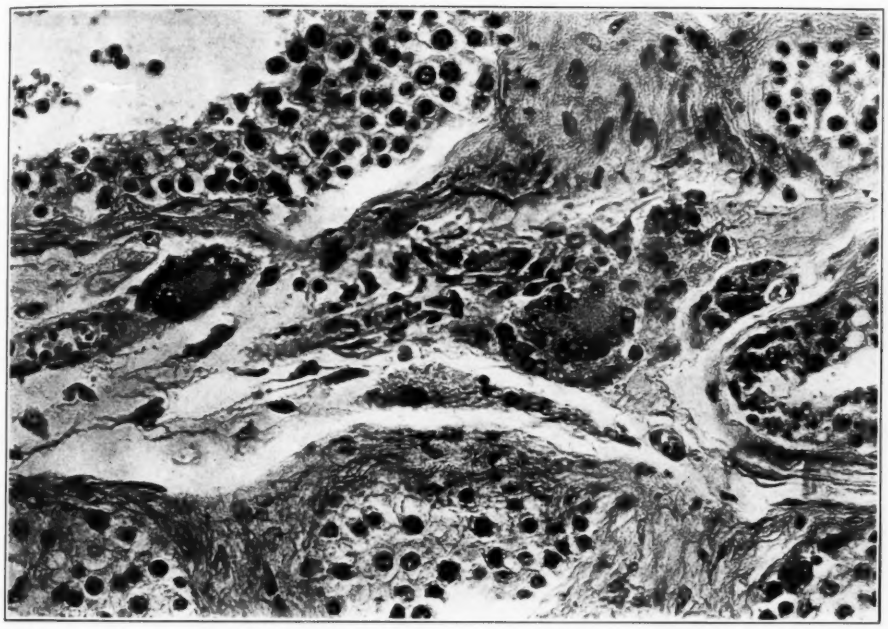
DESCRIPTION OF PLATES

PLATE 154

FIG. 1. Case 296. 72 years; cerebral thrombosis. Group of giant interstitial cells among mononuclear interstitial cells. The pigment zone and clear center of the giant cells are well shown, as is the similarity of their nuclei to those of the ordinary interstitial cells. Hematoxylin-eosin. × 325.

FIG. 2. Case 194. 60 years; cerebral hemorrhage. Giant interstitial cell with 21 nuclei; one of the nuclei is more vesicular than the others. To the right are three mononuclear interstitial cells. Hematoxylin-eosin. × 650.

FIG. 3. Case 231. 65 years; coronary sclerosis. Giant interstitial cell with 14 nuclei. To the right are several mononuclear interstitial cells. Hematoxylin-eosin. × 650.



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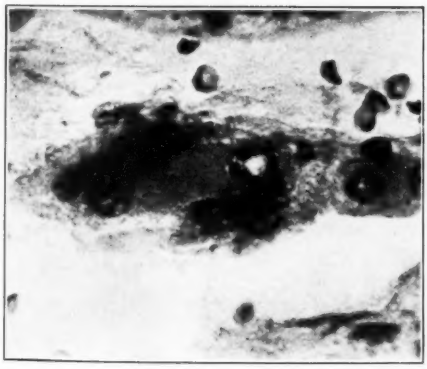

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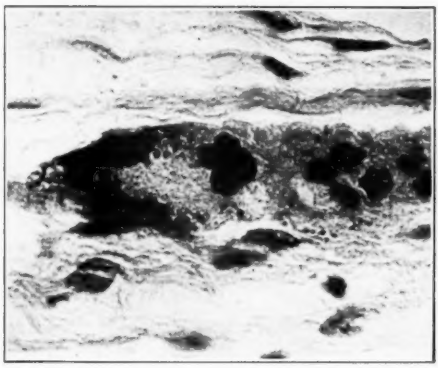


3

Nelson

Giant Interstitial Cells of Testis

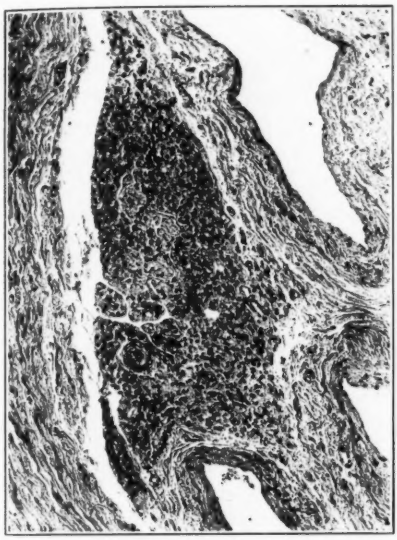
PLATE 155

FIG. 4. Case 231. Giant interstitial cell with 8 nuclei in tunica albuginea of the same testis as shown in Figure 3. Hematoxylin-eosin. × 800.

FIG. 5. Case 499. 82 years; hypertension. Large mass of extraparenchymal interstitial cells surrounding nerve fiber bundles in hilar region. Hematoxylin-eosin. × 60.

FIG. 6. Case 335. 66 years; polycystic kidneys. Small mass of pigmented extraparenchymal interstitial cells around a nerve in the tunica albuginea. This is the usual size of group seen. Hematoxylin-eosin. × 330.

FIG. 7. Case 547. 77 years; exfoliative dermatitis. Group of extraparenchymal interstitial cells in the tunica albuginea, containing numerous Reinke crystals and in association with a nerve. Azocarmine. × 465.



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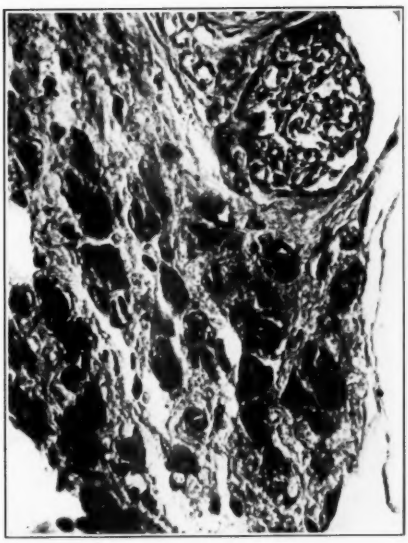

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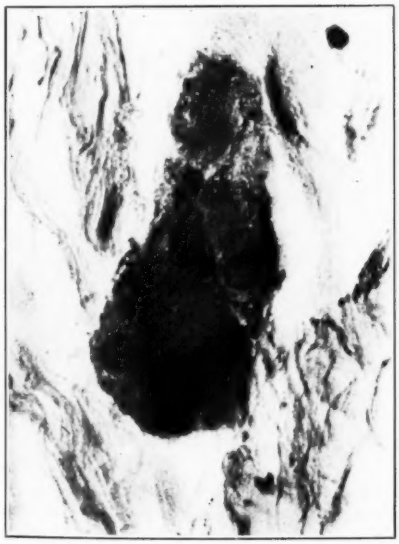

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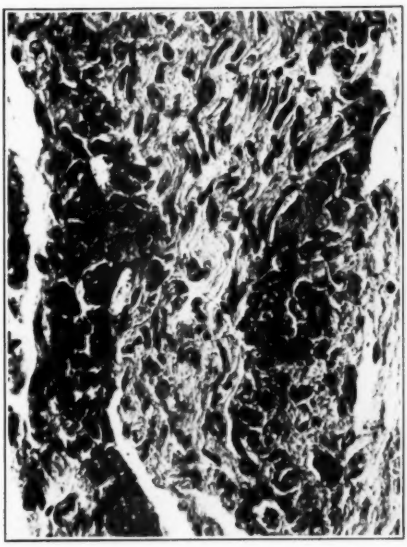

6

Nelson

Giant Interstitial Cells of Testis

THE EFFECT OF ASCORBIC ACID DEFICIENCY ON ENAMEL FORMATION IN THE TEETH OF GUINEA PIGS *

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The effect on enamel formation of diets deficient in ascorbic acid has received relatively little attention. Changes in this tissue are not mentioned in the classical work of Höjer [1] or of Wolbach and Howe,[2] although alterations in the dentin and dental pulp are described in detail. Kotányi [3] reported alterations of both the enamel-forming cells and the enamel itself in the teeth of scorbutic guinea pigs. Recently Fish and Harris [4] have emphasized that the changes in the enamel-forming cells in "full scurvy" are characteristic of the scorbutic process, although they were unable to demonstrate changes in these cells in "subscurvy." Their conclusion that "the failure of normal enamel formation, to which we find vitamin C deficiency gives rise, may be of significance in the causation of human caries" has been widely quoted.

Since the ameloblasts are of ectodermal origin, demonstration that a deficiency of ascorbic acid has a primary effect on these cells would constitute an exception to the findings of Wolbach [2, 5] that lesions caused by this deficiency are a consequence of the inability of certain cells of mesenchymal origin to produce and maintain normal intercellular substances and that other effects are secondary. Furthermore, evidence purporting to bear on the disputed etiology of dental caries should be thoroughly scrutinized.

MATERIAL AND METHODS

Ground and decalcified sections of the teeth of a large number of guinea pigs were examined.[6] Sections in cross and longitudinal planes of both incisor and molar teeth were stained routinely with hematoxylin and eosin. Mallory's aniline blue collagen stain and the phosphotungstic acid hematoxylin method were also fre-

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quently employed, and many sections were prepared by the Gömöri technique.[7]

Findings

Enamel deposition in the continually growing molar and incisor teeth of the guinea pig commences shortly after the first dentin is deposited. Enamel is laid down peripherally to the dentin until it reaches its maximum thickness at a point about one-third of the distance from the formative end (apex) to the end in function with its opponents of the opposite jaw (incisal or occlusal surface). At this point the enamel organ of the molar teeth is invaded by mesenchymal cells. Over the enamel surfaces surrounded by alveolar bone these cells deposit blocks of cementum which serve as attachments for the suspending fibers of the periodontium. Between the folds of the molar teeth a peculiar cartilage cement is deposited upon the enamel surfaces.

In the incisor teeth the enamel-forming cells become reduced in height after enamel deposition ceases, although they remain distinguishable until near the gingival crevice where they become merged with the cells of the oral epithelium. The cementum covers only a small part of the enamel surface on the buccal and lingual sides of the tooth. As has been previously pointed out,[8] the enamel covered area of the incisor teeth plays little part in the suspension of the teeth from the surrounding bone.

Enamel, as first deposited in both the molar and the incisor teeth, resists decalcification and stains deeply with basic dyes (Fig. 1). As the enamel approaches maturity it becomes partially decalcified when treated with 5 per cent nitric acid. The extreme complexity of the pattern made by the interwoven enamel rods becomes evident at this stage (Fig. 2). The outer border of the immature enamel remains unstained by the silver nitrate of the Gömöri technique (Fig. 3).

Careful examination of both ground and decalcified sections reveals that, contrary to Santoné,[9] many of the dentinal fibrils continue into the enamel. When stained by Mallory's aniline blue collagen stain the fibrils are colored a brilliant red. They are very fine, form a plexus in the outer part of the dentin and then angulate sharply to follow the course of the enamel rods so that they are difficult to trace.

Normally the width of the enamel is less than the width of the underlying dentin. The ratio of enamel to dentin is approximately 3:4.

Animals maintained on diets completely deficient in ascorbic acid show marked retardation of dentin deposition while enamel is deposited at approximately the normal rate. The dentin-forming cells are characteristically atrophic, while the enamel-forming cells appear normal (Fig. 4). The thickness of the enamel is accordingly several times greater than that of the corresponding dentin. Ratios of enamel to dentin vary from 3:1 to 4:1 (Figs. 4 and 5). When animals are maintained on diets completely deficient in ascorbic acid but supplemented with small amounts of this substance administered daily, the width of the enamel as compared to the dentin approaches normal as the dosage is increased (Figs. 6 and 7). Animals receiving 2 mg. or more daily have normal enamel and dentin. In both complete and partial deficiencies the enamel may show areas of hypoplastic structure. Such areas usually are associated with hemorrhage in the overlying tissues and with disruption and atrophy of the enamel-forming cells (Figs. 8, 9 and 10).

The periodontal tissues over the cementum covered parts of the tooth also show areas of hemorrhage and a diminution in the number of collagen fibers (Figs. 11, 13 and 14). Such regions appear cellular in comparison with the periodontal tissue of the normal animal (Fig. 15). Nevertheless, mitotic figures among these fibroblasts in ascorbic acid deficient animals are rare. When ascorbic acid is administered repair may be very rapid as indicated by numerous mitoses (Fig. 12).

Discussion

Loosening of the teeth has long been recognized as a cardinal sign of scurvy, both in man and in the experimental animal. This phenomenon occurs as the result of inability of the fibroblasts of the periodontium to form the collagen fibers by which the teeth are suspended from the surrounding bone and the corresponding inability of the osteoblasts and cementoblasts to form normal matrices for the attachment of these fibers.

Enamel formation is normally carried on in a protected environment. In the teeth of man the enamel is completely formed before

eruption into the oral cavity occurs. The deciduous teeth are so placed as to give added protection to their permanent successors while the latter are developing. It is a well known clinical observation that the premature extraction of the deciduous teeth may so injure the enamel-forming cells of the underlying permanent tooth that an area of hypoplastic enamel results.

Enamel formation in the constantly growing teeth of the guinea pig occurs while the teeth are in function. The mechanisms by which the forces of mastication are absorbed and dissipated in the part of the periodontium nearest the occlusal surface of the teeth while the formative part of the periodontium is protected from trauma has been the subject of a recent report.[10] It was concluded that a protected environment for the formation of enamel exists and that the collagenous suspending fibers play an important part in its maintenance. Failure of collagen fiber formation, the characteristic phenomenon of ascorbic acid deficiency, allows the transmission of excess forces to the formative part of the periodontium, adequately accounting for the areas of defective enamel formation described. Thus, enamel hypoplasia is a secondary rather than a primary consequence of the deficiency and corresponds to the hypoplasias of human teeth produced by trauma to the enamel organ.

Since the enamel of human teeth is formed before the teeth erupt into the oral cavity, the tooth germs are not exposed to masticatory forces while enamel is being deposited. Study of the tooth germ in infantile scurvy [11] and examination of the permanent teeth of a limited number of patients who recovered from infantile scurvy indicate that enamel hypoplasia does not result from ascorbic acid deficiency during the period of tooth formation. As in the guinea pig, though to a much less degree, dentin formation may be retarded so that the enamel may be of greater width than the underlying dentin, leading to the formation of a dwarfed crown covered with normal enamel.

Dental caries of the exposed dentin and cementum occurs in both incisor and molar teeth of the guinea pig.[12] However, no correlation with deficiency of the diet has been found. Caries of the normal or hypoplastic enamel has not been observed.

The clinical reports of Aschoff and Koch [13] and of Westin [14] indicate that a possible immunity rather than an increased suscep-

tibility to dental caries occurs in ascorbic acid deficiency in human beings.

From the evidence at present available, dental caries in man and in the guinea pig does not appear to be due to a deficiency of ascorbic acid in the diet.

Summary and Conclusions

1. Enamel formation is not primarily affected by ascorbic acid deficiency. Areas of hypoplastic enamel formation observed in both complete and partial ascorbic acid deficiency are adequately accounted for by the failure of collagen fibers and bone matrix to form in the periodontal tissues.

2. Enamel-dentin thickness ratios greater than 1 in ascorbic acid deficiency result from continuation of enamel formation at approximately the normal rate while dentin formation is retarded.

3. Satisfactory evidence of the relation between ascorbic acid deficiency and dental caries has not been established.

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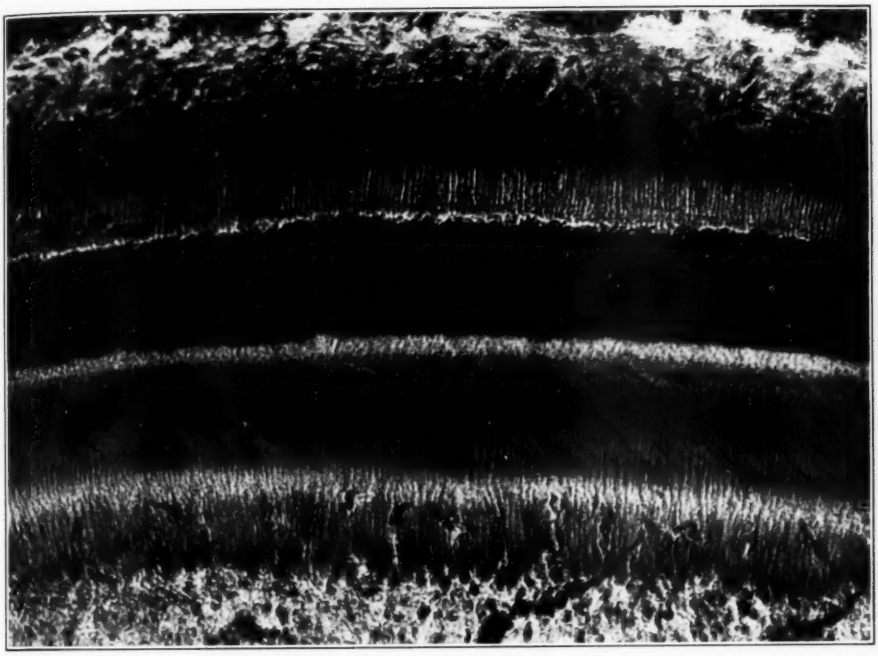
DESCRIPTION OF PLATES

Plate 156

Fig. 1. Guinea pig 76. Normal control animal. Early stage of enamel and dentin formation. Enamel-dentin ratio 3:4. Structures from above downward are vascular connective tissue, enamel organ, enamel, dentin, odontoblasts, and cells of the dental pulp. × 270.

Fig. 2. Guinea pig 77. Normal control animal. Later stage of enamel and dentin formation. Enamel-dentin ratio 3:4. × 270.



1

2

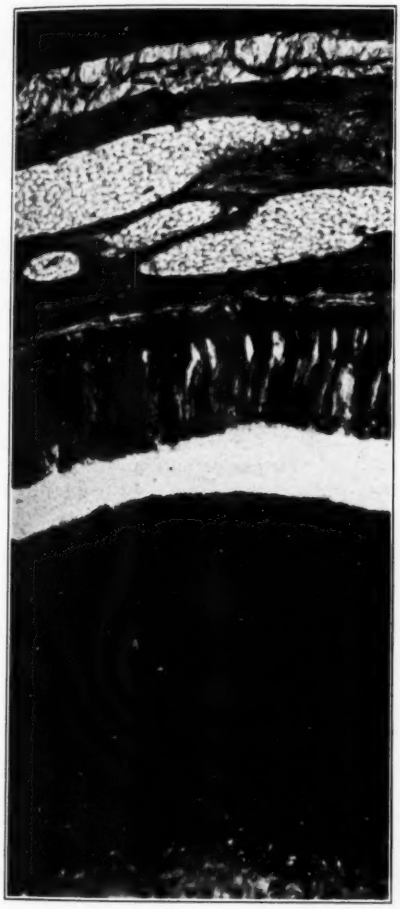
Boyle Effect of Ascorbic Acid Deficiency

PLATE 157

FIG. 3. Guinea pig 93, 109 days on the basal diet plus greens (positive control). The section was prepared by the Gömöri technique and shows the zone immediately beneath the ameloblasts unstained by silver nitrate. Structures in same order as in Figure 1. × 300.

FIG. 4. Guinea pig 152, 28 days on a diet free of ascorbic acid. The enamel-forming cells and the enamel itself are normal, while the odontoblasts and the dentin show the extreme atrophy characteristic of this deficiency. Structures from above downward are the alveolar bone, loose fibrous tissue with large blood vessels, enamel organ and its ameloblasts, enamel, dentin, odontoblasts, and cells of the dental pulp. × 300.

FIG. 5. Guinea pig 113. Basal diet alone for 28 days. Early stage of enamel and dentin formation. Dentin formation has been retarded while enamel deposition has taken place normally, resulting in a relatively wide enamel layer. Enamel-dentin ratio 3:1. × 300.



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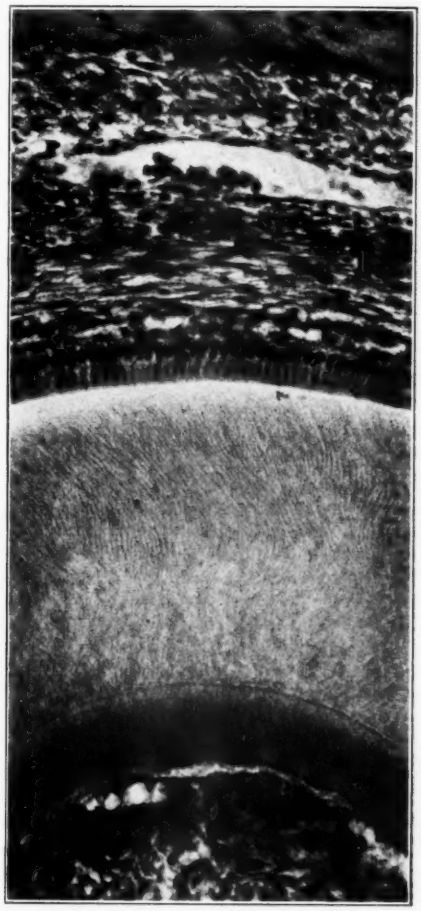

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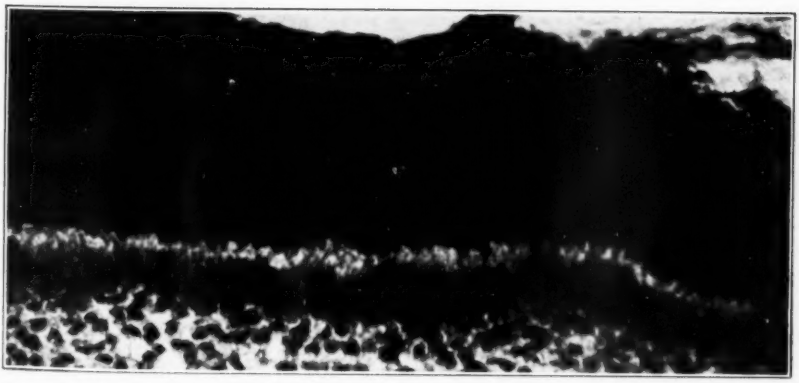

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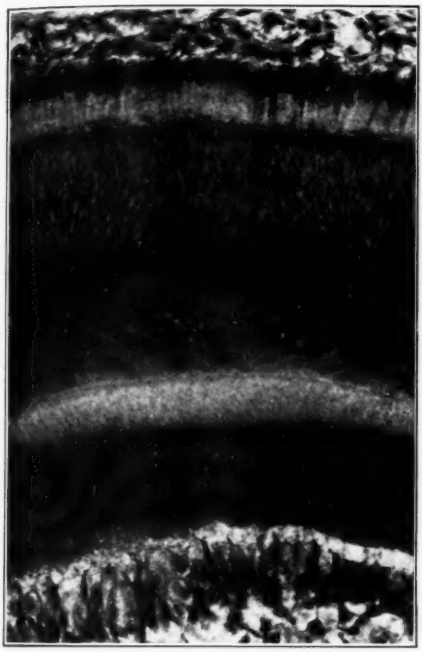
Effect of Ascorbic Acid Deficiency

PLATE 158

FIG. 6. Guinea pig 66. Basal diet supplemented by 0.5 mg. of ascorbic acid daily for 182 days. Enamel-dentin ratio 2:1. × 300.

FIG. 7. Guinea pig 140. Basal diet supplemented by 0.3 mg. of ascorbic acid daily for 329 days. Enamel-dentin ratio 4:1. × 300.

FIG. 8. Guinea pig 113. Basal diet for 28 days. Hypoplastic enamel formation. Atrophy of ameloblasts in region of irregular enamel deposition and hemorrhage in the overlying tissues. × 300.



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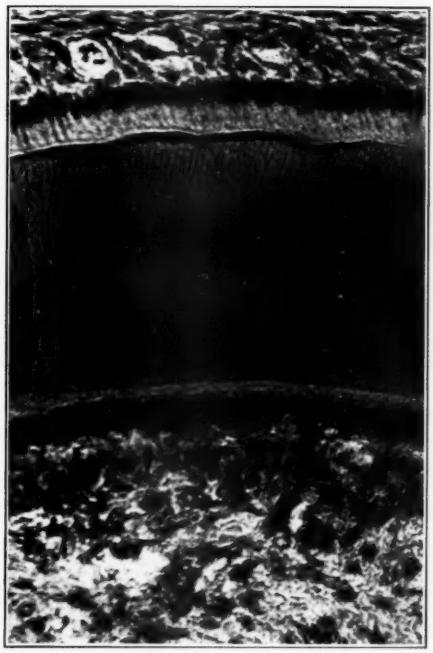

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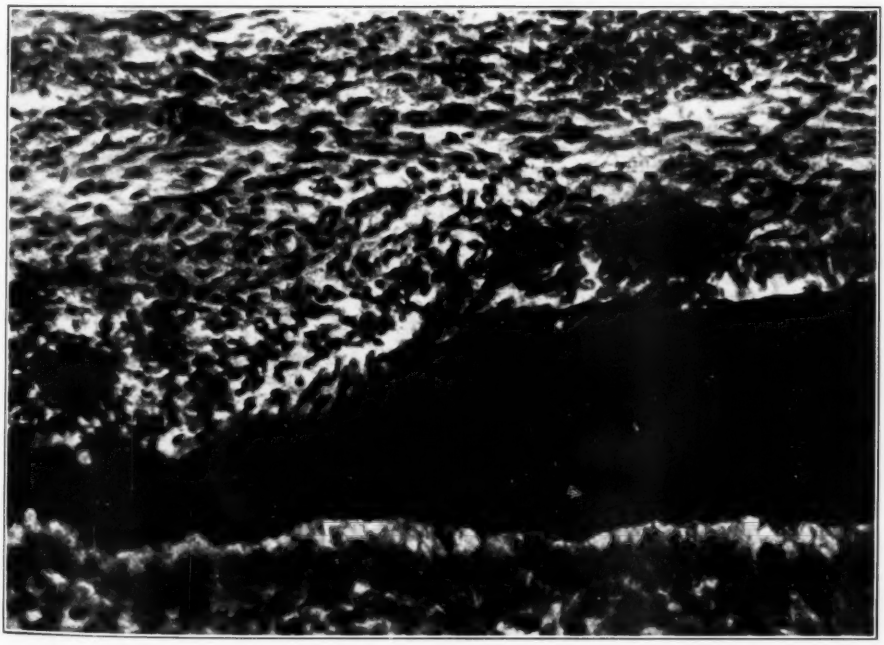

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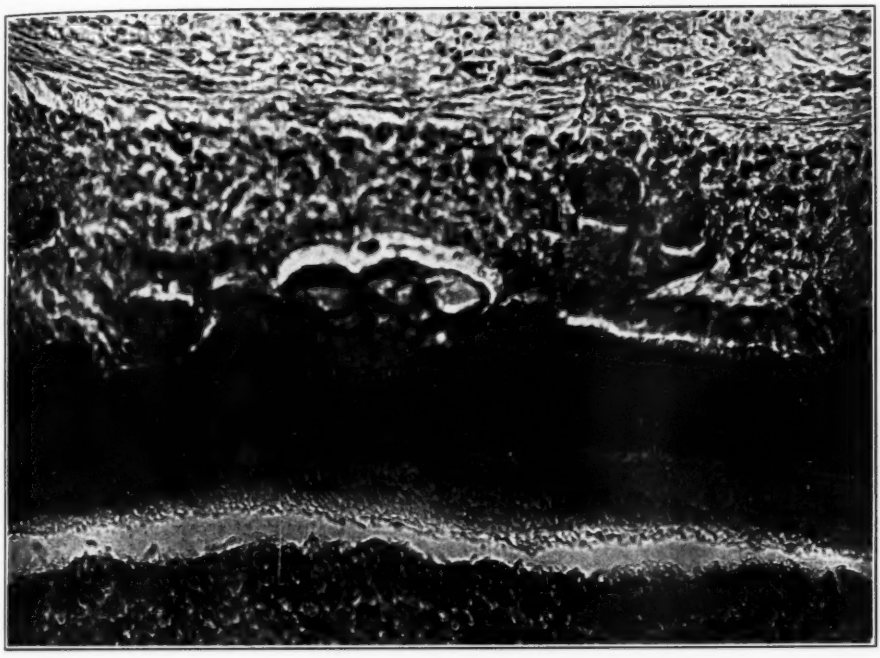
PLATE 159

FIG. 9. Guinea pig 152. Basal diet for 28 days. Area of hypoplastic enamel formation. × 300.

FIG. 10. Guinea pig 18. Basal diet supplemented by 1 mg. of ascorbic acid daily for 120 days. Area of hypoplastic enamel formation with atrophy of the ameloblasts and hemorrhage in the overlying tissues. This is a relatively rare finding in animals receiving more than 0.5 mg. of ascorbic acid daily. The enamel-dentin ratio elsewhere than in this area was normal (3:4). × 300.



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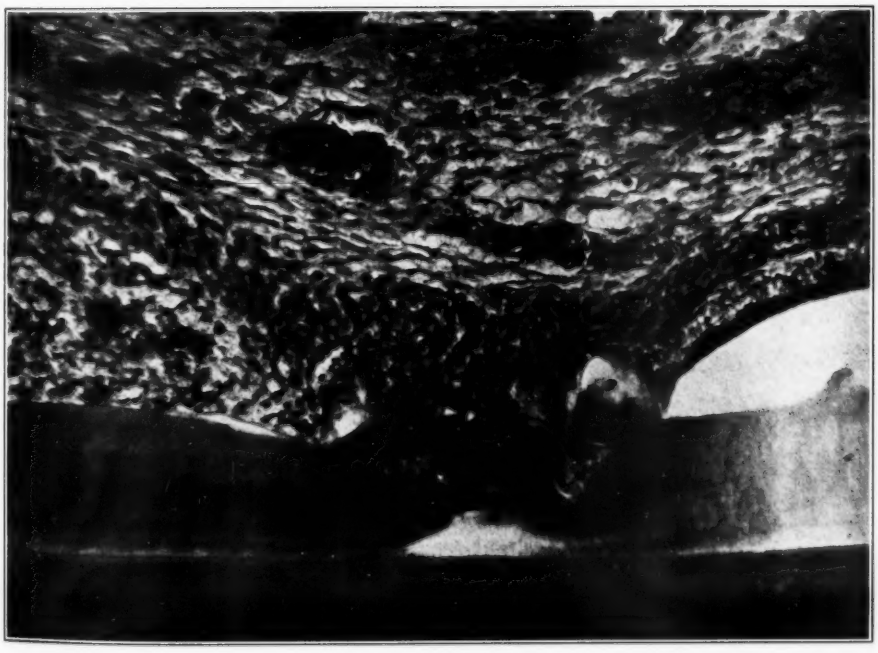

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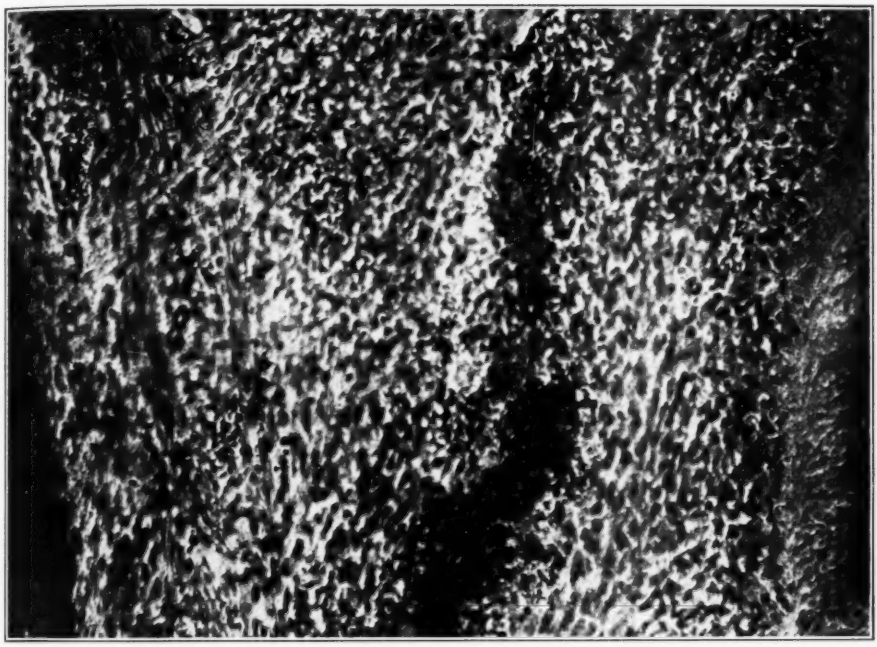
PLATE 160

FIG. 11. Guinea pig 152. Hemorrhage in the peridental tissues on the cementum side of the tooth opposite the hypoplastic area is shown in Figure 9. × 300.

FIG. 12. Guinea pig 116. Basal diet for 35 days, 100 mg. of ascorbic acid by mouth in 2 doses, killed 48 hours after the 1st dose. Active repair in the fibrous tissue overlying the cementum. Note the mitotic figures. × 300.



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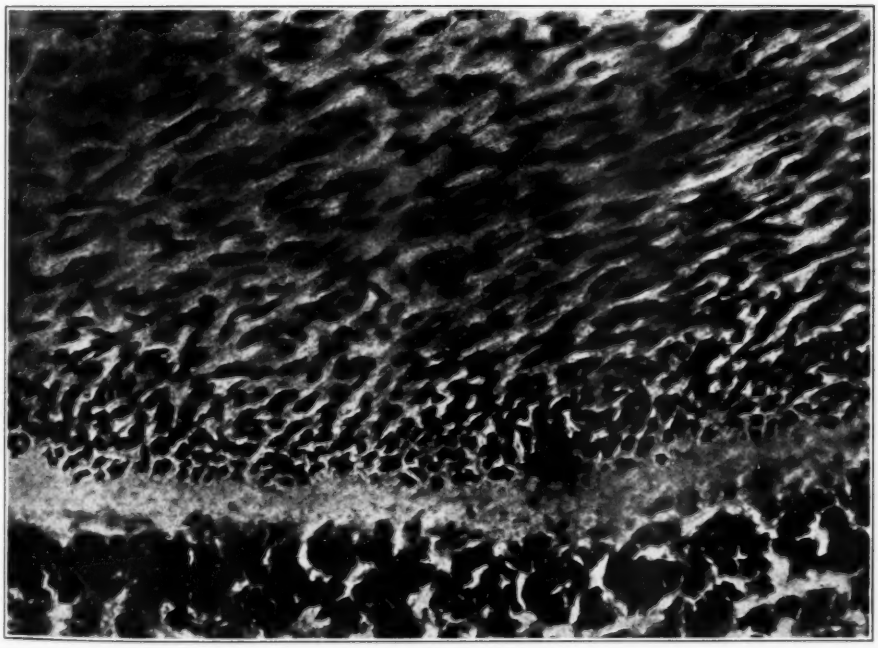

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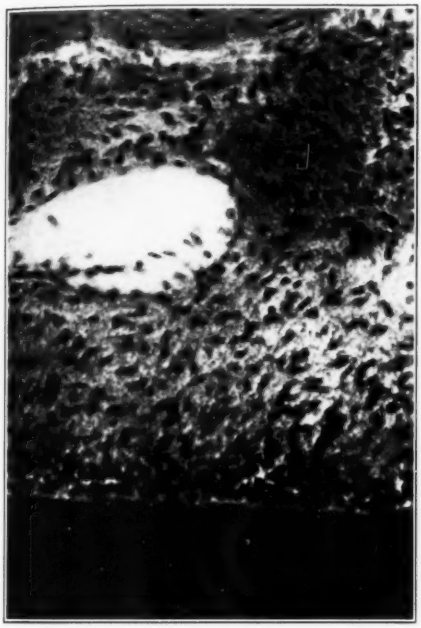
PLATE 161

FIG. 13. Guinea pig 31. Basal diet for 27 days. Fibrous tissue connects the overlying alveolar bone with the cementum covered surface of the tooth. The cells are atrophic and collagen fibers are lacking or represented by a granular intercellular material. × 300.

FIG. 14. Guinea pig 141. Basal diet supplemented by 0.3 mg. of ascorbic acid daily for 252 days. Many of the fibroblasts show vacuoles and the cementum is hyperplastic in response to loosening of the tooth. × 300.

FIG. 15. Guinea pig 94. Basal diet supplemented by 5 mg. of ascorbic acid daily for 121 days (positive control). The bone, fibrous tissue, cementum and dentin are normal in structure. × 300.



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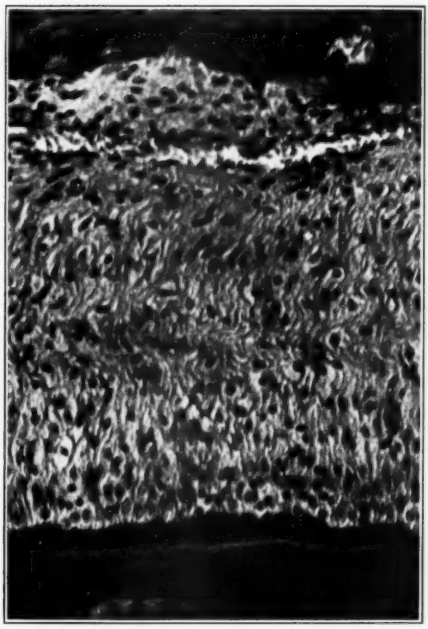

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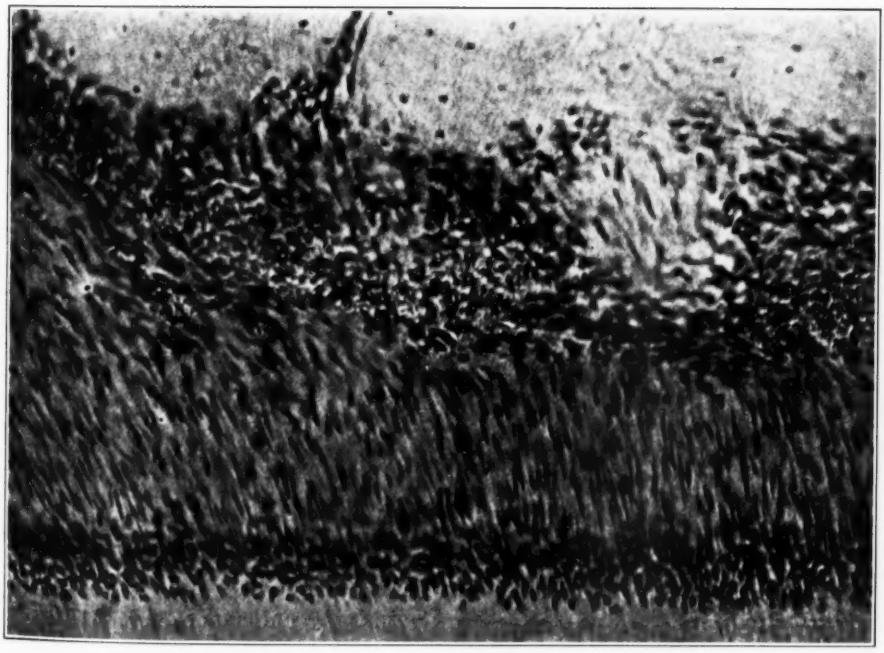

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